Streptococcus pneumoniae meningitis in Alberta pre- and postintroduction of the 7-valent pneumococcal conjugate vaccine

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J Johnstone, GJ Tyrrell, TJ Marrie, S Garg, JD Kellner; the *Streptococcus pneumoniae* Alberta Team (SPAT) group. *Streptococcus pneumoniae* meningitis in Alberta pre- and postintroduction of the 7-valent pneumococcal conjugate vaccine. Can J Infect Dis Med Microbiol 2011;22(4):137-141.

OBJECTIVE: To describe the epidemiology, clinical characteristics, microbiology and outcomes of patients of all ages with *Streptococcus pneumoniae* meningitis two years pre- and postintroduction of a *S pneumoniae* 7-valent conjugate vaccine program in Alberta in children <2 years of age.

METHODS: Between 2000 and 2004, all cases of invasive pneumococcal disease in Alberta were identified. From this cohort, patients with *S pneumoniae* meningitis were identified by chart review. Clinical data, laboratory data and in-hospital outcomes were collected.

RESULTS: Of the 1768 cases of invasive pneumococcal disease identified between 2000 and 2004, 110 (6.2%) had *S pneumoniae* meningitis. The overall incidence was 0.7 per 100,000 persons and remained unchanged over the study period. The rate in children <2 years of age appeared to fall over time, from 10.5 per 100,000 persons in 2000 to five per 100,000 persons in 2004, although there was insufficient evidence of a statistically significant time trend within any age group. Overall, the mean age was 30 years and 47% were male. In-hospital mortality was 20%, ranging from 6% in those ≤2 years of age to 31% for those ≥18 years of age, despite appropriate antimicrobial therapy.

CONCLUSION: The high mortality rate associated with *S pneumoniae* meningitis suggests that prevention by vaccination is critical. In children <2 years of age, there was a downward trend in the rate of *S pneumoniae* meningitis after implementation of the *S pneumoniae* 7-valent conjugate vaccine program, but rates were still high.

Key Words: *Conjugate; Meningitis,* Streptococcus pneumoniae; *Vaccine*

La méningite à *Streptococcus pneumoniae* en Alberta avant et après l'adoption du vaccin conjugué heptavalent contre le pneumocoque

OBJECTIF : Décrire l'épidémiologie, les caractéristiques cliniques, la microbiologie et les issues de patients de tout âge atteints de méningite à *Streptococcus pneumoniae* deux ans avant et après l'adoption, en Alberta, d'un programme de vaccination contre le *S pneumoniae* par le vaccin conjugué chez les enfants de moins de deux ans.

MÉTHODOLOGIE : De 2000 à 2004, les chercheurs ont retracé tous les cas de maladie pneumococcique invasive en Alberta. Dans cette cohorte, ils ont dépisté les patients atteints de méningite à *S pneumoniae* par étude des dossiers. Ils ont colligé les données cliniques, les données de laboratoire et les issues des hospitalisations.

RÉSULTATS : Des 1 768 cas de maladie pneumococcique invasive dépistés entre 2000 et 2004, 110 (6,2 %) étaient atteints de méningite à *S pneumoniae*. L'incidence globale était de 0,7 cas sur 100 000 personnes et est demeurée inchangée pendant la période de l'étude. Le taux chez les enfants de moins de deux ans semblait reculer au fil du temps, passant de 10,5 cas sur 100 000 personnes en 2000 à cinq cas sur 100 000 personnes en 2004, même si les données probantes de tendance statistiquement significative étaient insuffisantes dans l'un ou l'autre des groupes d'âge. Dans l'ensemble, l'âge moyen était de 30 ans, et 47 % étaient de sexe masculin. La mortalité en milieu hospitalier s'élevait à 20 %, passant de 6 % chez les enfants de deux ans et moins à 31 % chez ceux de 18 ans et plus, malgré un traitement antimicrobien pertinent.

CONCLUSION : Le fort taux de mortalité associé à la méningite à *S pneumoniae* laisse supposer qu'il est essentiel de prévenir la maladie par la vaccination. Chez les enfants de moins de deux ans, on remarque une tendance décroissante du taux de méningite à *S pneumoniae* après l'adoption du programme de vaccination contre le *S pneumoniae* par le vaccin conjugué heptavalent, mais le taux demeurait tout de même élevé.

Infection due to *Streptococcus pneumoniae* is a significant cause of morbidity and mortality worldwide (1,2). Meningitis is a serious manifestation of *S pneumoniae,* with a case fatality rate of approximately 20% in adults (3). The mortality rate in children is lower (5%); however, a large proportion (37%) of children have neurological sequelae (2,4). In North America, *S pneumoniae* is the most common bacterial cause of meningitis (5), and the incidence is highest in children <2 years of age (6).

In 2000, a heptavalent protein-polysaccharide conjugate vaccine (PCV-7; Prevnar [Pfizer Inc, USA]) was first licensed in the United States for use in infants and children. PCV-7 is currently recommended in North American immunization guidelines for routine use in children <2 years of age (7,8). PCV-7 is targeted against *S pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F; these serotypes account for 80% of invasive pneumococcal disease (IPD) in children <6 years of age (8). In Canada, the province of Alberta was the first to introduce a universal childhood vaccination program against *S pneumoniae,* with a four-dose schedule administered at two, four, six and 18 months of age in September 2002 (9). All infants born on July 1, 2002, and onwards were eligible to receive PCV-7 (10). It is estimated that 90% of children received three doses of PCV-7 by 12 months of age, and approximately 80% received all four doses by

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24 months of age (10). There was no catch-up program implemented in Alberta.

Studies evaluating the effectiveness of PCV-7 have demonstrated a substantial decline in IPD among vaccine-eligible children, first in the United States and Canada, and more recently in other countries (11-14). There have also been declines in vaccine serotype IPD in older children and adults: two populations that have not received PCV-7 (11,12,15,16). It is hypothesized that this overall decline in vaccine serotype IPD is secondary to an indirect herd effect of PCV-7 vaccination (4,11,15,16). The declining rate of IPD has corresponded with a declining rate of *S pneumoniae* meningitis due to vaccine serotypes among children (11,17) and adults (18).

Studies investigating the changing incidence of *S pneumoniae* meningitis have not included detailed clinical data (11,15-18). Thus, we sought to describe the epidemiology, clinical characteristics, microbiology and outcomes of all age groups of patients with *S pneumoniae* meningitis over a five-year period, and to identify whether implementation of PCV-7 impacted the incidence of *S pneumoniae* meningitis in children and adults in Alberta. We also sought to determine the proportion of *S pneumoniae* meningitis caused by serotypes included in the next generation 10-valent and 13-valent pneumococcal conjugate vaccines.

METHODS

Demographics and data collection

The period under review was January 1, 2000, to December 31, 2004, and encompassed the entire province of Alberta. The population of Alberta was 2,967,755 in 2000, and 3,179,036 in 2004 (19). Since 1998, IPD has been categorized as a notifiable disease in Alberta; therefore, all IPD cases in the province are to be reported to the Provincial Health Office. The definition of IPD followed the Canadian national case definition for IPD: isolation of *S pneumoniae* from a normally sterile site such as blood, cerebral spinal fluid, pleural fluid, biopsy tissue, joint aspiration, pericardial fluid or peritoneal fluid (20). All identified *S pneumoniae* isolates from IPD cases in Alberta are also to be forwarded from acute diagnostic microbiology laboratories to the National Centre for Streptococcus (NCS) in Edmonton, Alberta, for serotyping. To ensure completeness of case ascertainment, all cases from the following public health and research databases were combined: IPD isolates sent to the NCS; IPD cases reported to the Provincial Health Office; IPD cases captured by the Calgary Area *S pneumoniae* Epidemiology Research (CASPER) team; and IPD cases captured by the Community Acquired Pneumonia Study (Edmonton). Each case was only counted once, and cases whose home address was outside of Alberta were excluded.

An extensive retrospective chart review of all identified cases of IPD was performed during the survey period to determine demographic data, pre-existing clinical conditions, features of the clinical presentation, clinical course and outcome. From this cohort, patients with *S pneumoniae* meningitis were identified. Cases were defined as having meningitis if *S pneumoniae* was isolated from cerebrospinal fluid, or *S pneumoniae* was isolated from the blood and a diagnosis of meningitis was recorded on the patient's medical record. The present study was approved by the Ethics Review Committees of all nine health regions in Alberta, and at the University of Alberta (Edmonton) and University of Calgary (Calgary, Alberta).

Serotyping of pneumococcal isolates

Isolates received at the NCS were confirmed as *S pneumoniae* using optochin susceptible and bile solubility assays (21). Serotyping of all *S pneumoniae* isolates was performed at the NCS using the Quellung reaction, which used *S pneumoniae* serotyping antisera obtained from the Statens Serum Insititut in Copenhagen, Denmark (22). The 10-valent protein-polysaccharide conjugate vaccine (PCV-10 [GlaxoSmithKline Inc, Canada]) includes all serotypes in the PCV-7 vaccine plus 1, 5 and 7F; the 13-valent protein-polysaccharide conjugate vaccine (PCV-13 [Pfizer Inc]) includes all serotypes in the PCV-7 vaccine plus 1, 3, 5, 6A, 7F and 19A.

Antimicrobial susceptibility assays

Antibiotic susceptibility was determined using standard reference broth microdilution (23). Penicillin, cefotaxime, ceftriaxone and vancomycin were assayed. All antimicrobial agents were purchased from Sigma-Aldrich Canada Ltd. The minimum inhibitory concentrations (MICs) were used to interpret susceptibility for *S pneumoniae* as per standard guidelines that were current at the time of the study (23).

Statistical analysis

Descriptive statistics were expressed as mean ± SD or median (interquartile range) for continuous variables and proportions (%) for categorical variables. Unadjusted patient characteristics and outcomes were described according to age group (<2 years, two to four years, five to 17 years and ≥18 years). For overall PCV-7 and non-PCV7 incidence sets, Poisson regression models with age at the time of infection, linear calendar time (2000 to 2004), and interaction between age and time were used to evaluate any possible time trends and their statistical significance. All tests were two sided, and the alpha level of significance was set at 0.05. Data were analyzed using SAS software, version 9.1 (SAS Institute Inc, USA).

RESULTS

Between 2000 and 2004, 2005 cases of IPD were reported to the Provincial Health Office in Alberta. Of these, complete clinical data were obtained from 1768 cases, and 110 (6.2%) of these cases had meningitis.

S pneumoniae meningitis incidence and serotypes

The overall incidence of *S pneumoniae* meningitis in Alberta between 2000 and 2004, was 0.7 per 100,000 persons. The highest incidence was in children younger than two years (8.8 per 100,000 persons) (Table 1). In contrast, the incidence was 1.7 per 100,000 persons in the two- to four-year age group, 0.3 per 100,000 persons in the five- to 17-year group and 0.5 per 100,000 persons in the ≥18-year age group (Table 1). The rate of *S pneumoniae* meningitis in those <2 years of age was 10.5 per 100,000 persons in 2000, and five per 100,000 persons in 2004 (Figure 1). The rate of vaccine serotype meningitis in this age group decreased from 10.5 per 100,000 persons in 2000 to 1.2 per 100,000 persons in 2004 (Figure 2), whereas the rate of nonvaccine serotype meningitis in those <2 years rose from zero per 100,000 persons in 2000, to 3.7 per 100,000 persons in 2004 (Figure 3). The rates of *S pneumoniae* meningitis in all other age groups remained essentially unchanged over the study period (Figures 1, 2 and 3). Although all three models (overall incidence, PCV-7 serotype incidence and non-PCV-7 serotype incidence) showed significant differences in incidence between age groups (P<0.0001 for all three models), there was insufficient evidence of a statistically significant time trend within any age group (P>0.05 for all three models).

In total, *S pneumoniae* meningitis was caused by 32 different serotypes. The three most common serotypes were 14 (14%), 6B (14%) and 18C (10%). Five per cent of meningitis cases were caused by serotype 19A. These occurred throughout the study period: one in 2001, two in 2002, one in 2003 and one in 2004. Overall, 55% of all meningitis cases were due to PCV-7 serotypes; however in children <2 years of age, this proportion increased to 74% and to 80% in the two- to four-year age group (Table 1). The proportion of meningitis cases caused by serotypes included in PCV-10 and PCV-13 was higher when compared with the proportion covered by PCV-7 (Table 1).

Presenting clinical characteristics

In the 110 patients with *S pneumoniae* meningitis, the mean ± SD age was 30±28 years; 47% were male, and 7% were Aboriginal (Table 2). There were 34 cases in children <2 years of age (23 preintroduction and 11 postintroduction of PCV-7) and 76 cases ≥2 years of age (39 preintroduction and 37 postintroduction of PCV-7). Eighty-seven per cent were bacteremic, 32% had concomitant pneumonia, 19% initially presented with otitis media and 21% with sinusitis (Table 2). Overall, only 38% had presence of the meningitis triad: fever,

TABLE 1
Incidence of *Streptococcus pneumoniae* meningitis and *S pneumoniae* serotypes*, stratified according to age group

	Total (n=110)	<2 y (n=34)	2–4 y (n=10)	5–17 y (n=8)	≥18 y (n=58)
Overall incidence	0.7	8.8	1.7	0.3	0.5
PCV7 serotypes	61 (55)	25 (74)	8 (80)	2 (25)	26 (45)
PCV10 serotypes	64 (58)	26 (76)	8 (80)	2 (25)	28 (48)
PCV13 serotypes	76 (69)	28 (82)	9 (90)	3 (38)	36 (62)

*Data presented as n (%) unless otherwise indicated. *Individual serotype data available on request. PCV Pneumococcal conjugate vaccine; y Years*

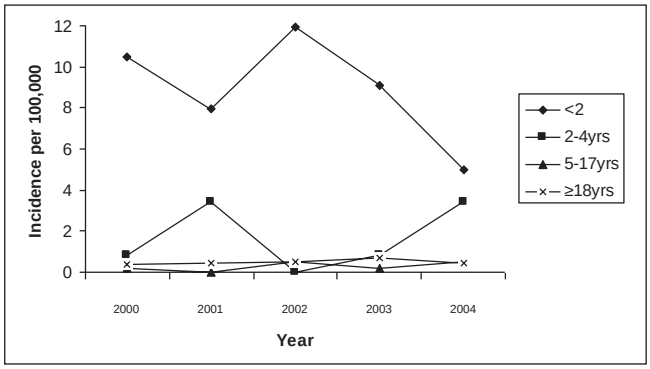

Figure 1) *Incidence of* Streptococcus pneumoniae *meningitis per 100,000 persons in Alberta, over five years (yrs), stratified according to age group*

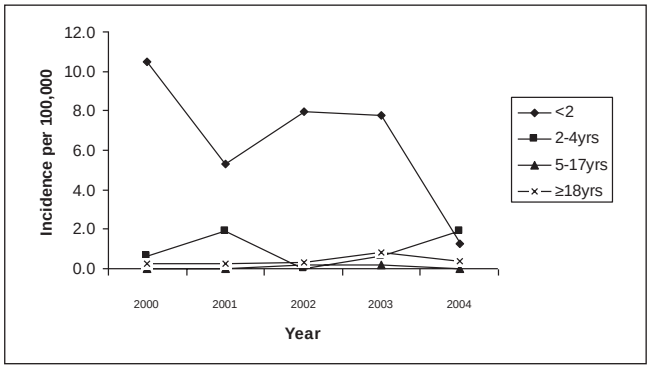

Figure 2) *Incidence of* Streptococcus pneumoniae *meningitis due to pneumococcal conjugate vaccine 7 serotypes per 100,000 persons in Alberta, over five years (yrs), stratified according to age group*

meningismus and altered mental status. However, 99% had at least one of the triad findings (Table 2). Other presenting features can be found in Table 2.

Antimicrobial susceptibility

Of the 110 isolates from *S pneumoniae* meningitis cases, 79 (72%) had complete susceptibility data available. All isolates (79 of 79) were susceptible to ceftriaxone (MIC <1.0 µg/mL) and vancomycin (MIC ≤0.5 µg/mL). Seventy-two (91%) isolates were susceptible to penicillin (MIC <0.1 µg/mL), six (8%) were intermediate (MIC 0.1 µg/mL to 1.0 µg/mL) and one (1%) was resistant (MIC >2.0 µg/mL).

Therapy

In terms of treatment, 78% were treated with ceftriaxone plus vancomycin, and 19% were treated with ceftriaxone alone. Ninety per cent of children (<18 years of age) received ceftriaxone plus vancomycin, whereas only 67% of adults (≥18 years of age) received dual therapy. Few patients (16%) received dexamethasone therapy as an adjunct to antibiotic therapy for meningitis; 14% were children (<18 years of age) and 19% were adults (≥18 years of age).

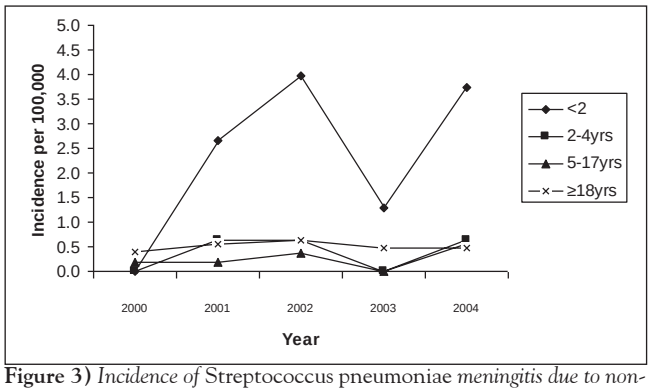

Figure 3) *Incidence of* Streptococcus pneumoniae *meningitis due to non-pneumococcal conjugate vaccine 7 serotypes per 100,000 persons in Alberta, over five years (yrs), stratified according to age group*

TABLE 2
Clinical characteristics of patients presenting with *Streptococcus pneumoniae* meningitis, stratified according to age group

Characteristic	Total (n=110)	<2 y (n=34)	2–4 y (n=10)	5–17 y (n=8)	≥18 y (n=58)
Sociodemographic					
Male	52 (47)	19 (56)	3 (30)	5 (62)	25 (43)
Aboriginal	8 (7)	4 (12)	0 (0)	0 (0)	4 (7)
Comorbidity					
Respiratory	20 (18)	3 (9)	1 (10)	1 (12)	15 (26)
Cardiac	23 (21)	3 (9)	1 (10)	0 (0)	19 (33)
Neurological	16 (15)	2 (6)	2 (20)	2 (25)	10 (17)
Renal disease	3 (3)	0 (0)	0 (0)	0 (0)	3 (5)
Concurrent *S pneumoniae* disease					
Bacteremia	96 (87)	32 (94)	9 (90)	8 (100)	47 (81)
Pneumonia	35 (32)	5 (15)	2 (20)	0 (0)	28 (48)
Encephalitis	5 (5)	0 (0)	1 (10)	0 (0)	4 (7)
Otitis media	21 (19)	4 (12)	3 (30)	1 (12)	13 (22)
Sinusitis	23 (21)	2 (6)	2 (20)	6 (75)	13 (22)
Signs					
Altered mental status	93 (85)	28 (82)	9 (90)	7 (88)	49 (84)
GCS (≤14)	61 (55)	8 (24)	7 (70)	4 (50)	42 (72)
New-onset seizures	29 (26)	14 (41)	3 (30)	1 (12)	11 (19)
Meningismus	57 (52)	16 (47)	6 (60)	7 (88)	28 (48)
Abnormal temperature (<35°C or ≥38°C)	98 (89)	34 (100)	10 (100)	8 (100)	46 (79)
Hypotension (<90 mmHg)	9 (8)	4 (12)	0 (0)	0 (0)	5 (9)
Classic triad*	42 (38)	14 (41)	5 (50)	6 (75)	17 (29)
Presence of one triad* finding	109 (99)	34 (100)	10 (100)	8 (100)	57 (98)
Investigations					
Positive CSF culture	93 (85)	28 (82)	9 (90)	7 (88)	49 (84)
Positive CSF Gram stain	85 (77)	25 (74)	8 (80)	6 (75)	46 (79)
Elevated CSF WBC	87 (79)	27 (79)	9 (90)	6 (75)	45 (78)
Low CSF glucose (<2.2 mmol/L)	62 (56)	17 (50)	4 (40)	5 (62)	36 (62)
High CSF protein (>0.45 g/L)	83 (75)	26 (76)	7 (70)	6 (75)	44 (76)
Treatment					
Ceftriaxone plus vancomycin	86 (78)	29 (85)	10 (100)	8 (100)	39 (67)
Ceftriaxone	21 (19)	3 (9)	0 (0)	0 (0)	18 (31)
Outcome					
ICU	68 (62)	15 (44)	10 (100)	5 (62)	38 (66)
Died	22 (20)	2 (6)	1 (10)	1 (12)	18 (31)

*Data presented as n (%). *Triad: Fever, meningismus and altered mental status. CSF Cerebrospinal fluid; GCS Glasgow coma scale; ICU Intensive care unit; mo Months; WBC White blood cell count; y Years*

Outcomes

The median length of stay was 13 days (interquartile range nine to 17 days), and 62% were admitted to the intensive care unit. The overall in-hospital mortality rate was 20%, ranging from 6% in those <2 years of age to 31% in those ≥18 years of age (Table 2).

DISCUSSION

The present study of 110 consecutive cases of *S pneumoniae* meningitis in Alberta over a five-year period (2000 to 2004) illustrates how *S pneumoniae* meningitis continues to affect all age groups, with a high case fatality rate of 20%. *S pneumoniae* meningitis most commonly affects children <2 years of age; however, the risk of death is highest in adults. Although there was a downward trend in the incidence of vaccine serotypes among those <2 years of age following the introduction of PCV-7 vaccine in 2002, the risk of *S pneumoniae* meningitis continues to be highest in this age group.

The declining rate of *S pneumoniae* meningitis among children <2 years of age following the introduction of PCV-7 vaccination has been well documented by other larger surveillance studies with comparable reductions in rates (56% to 66%) (17,18,24). The reduction in the rate of meningitis in this age group, particularly among PCV-7 serotypes, in our study was striking; it seems likely that significance was not achieved because of the small sample size.

A recent study by Tsai et al (17) observed a 51% decrease in *S pneumoniae* meningitis hospitalization rates among children two to four years of age, suggesting a lower incidence in children in this age group as a result of PCV-7 (17). This finding was not observed in our study, but the difference may be explained by the very small number of cases in this age group, although a recent large population-based surveillance study by Hsu et al (18) was also not able to confirm a decrease in rate in this age group due to a fewer number of cases.

Tsai et al also described a decline in the rate of *S pneumoniae* meningitis among adults and hypothesized that this was due to a herd effect – an indirect vaccine effect resulting from decreased nasopharyngeal carriage among children <2 years of age (4,17). Supporting this hypothesis, Hsu et al (18) also noted a significant decline in adult meningitis cases due to PCV-7 serotypes. The herd effect, however, does not appear to impact the overall incidence of meningitis in adults (18). This is not surprising because only 45% of adult meningitis cases in our study were due to PCV-7 serotypes.

The mortality rate of *S pneumoniae* meningitis has remained largely unchanged for the past 30 to 40 years despite advances in health care (25). The case fatality rate of 20% observed in our study is consistent with rates reported in the literature (3,6). The high mortality rate could not be explained by inappropriate antibiotic therapy. In general, guidelines recommend adding vancomycin to ceftrixone/cefotaxime because of emerging *S pneumoniae* ceftriaxone/cefotaxime resistance (26). Even though one-fifth of individuals received empirical ceftriaxone monotherapy, there were no cases of ceftriaxone resistance in our study.

The mortality rate of 31% in adults was notable; however, advanced age is a known risk factor for poorer outcomes in *S pneumoniae* meningitis (25,27). Poor outcomes have also been associated with new-onset seizures at presentation (27). In our study, seizures were common, occurring one-quarter of the time, consistent with previous studies (25,27). Unfortunately, neither one of these risk factors for poor prognosis are modifiable.

Interestingly, having an otogenic or sinusitis focus has been shown in a previous study to be associated with better survival (25). In our study, concurrent sinusitis or otitis media occurred approximately 20% of the time. Sinusitis, which in our study had to be confirmed by imaging, was surprisingly high in children five to 17 years of age, occurring 75% of the time. Concurrent otitis media occurred in 22% of adults with *S pneumoniae* meningitis, despite the fact that otitis media is uncommon in adults (28). Thus, a recent history of sinusitis or otitis media, particularly in teenagers or adults, may raise the index of suspicion of *S pneumoniae* meningitis in persons presenting with signs/symptoms suggestive of meningitis.

One way in which researchers have attempted to improve case fatality rates in meningitis is through the use of corticosteroids. In adults, randomized controlled trial evidence has shown a mortality benefit of corticosteroids when given before appropriate antibiotic therapy (29,30). Those with *S pneumoniae* meningitis derive the greatest benefit; guidelines currently recommend routine administration of dexamethasone before antibiotic therapy in adults with meningitis (26,29). In our study, which ended in 2004, only 19% of patients received dexamethasone, likely related to the fact that the randomized controlled evidence only emerged in 2002, and guideline recommendations were only implemented in 2004. There remains ongoing controversy over whether dexamethasone should be given to children with meningitis; only 14% of children in our study received the drug, likely reflecting this controversy (31-33).

The high case fatality rate associated with *S pneumoniae* meningitis suggests prevention is critical. Studies evaluating immunogenicity, efficacy and safety of novel pneumococcal conjugate vaccines are currently underway (34). PCV-10 and PCV-13 are two of several new pneumococcal conjugate vaccines. PCV-10 contains 10 *S pneumoniae* serotypes conjugated to *Haemophilus influenzae*-derived protein D, whereas PCV-13 uses the same protein carrier as PCV-7 (CRM_{197}), but covers five additional serotypes (35,36). In our study, a higher proportion of *S pneumoniae* meningitis was caused by serotypes contained in PCV-10 and PCV-13 than PCV-7 for all age groups. There are data suggesting that although serotypes 6A and 19A are not included in PCV-7, cross-protection against these serotypes may have been generated by immunological similarities to serotype 6B and 19F; however, the data supporting cross-protection against 6A from 6B are far more convincing than for 19A from 19F (37). The immunogenicity against 19A as a result of 19F appears to be insufficient to prevent colonization with 19A (37). This lack of protection may help explain the emergence of non-PCV-7 vaccine replacement serotypes, specifically the rising number of IPD cases due to serotype 19A (38,39). In our study, there were few cases of 19A, although follow-up was only for two years and it may be too early to see evolving serotype trends.

Although the present study had several strengths, there were some limitations. The clinical data were retrospectively obtained and, therefore, carries limitations inherent to retrospective design. This particularly impaired our ability to assess morbidity, especially due to neurological sequelae. The true incidence of *S pneumoniae* meningitis may have been underestimated; cases without a positive cerebral spinal fluid or blood culture would have been missed. Follow-up was limited to in-hospital outcomes and, therefore, longer-term mortality could not be obtained.

CONCLUSION

S pneumoniae meningitis is a life-threatening illness, which affects all age groups. The high mortality rate associated with *S pneumoniae* meningitis, despite appropriate therapy, suggests that prevention of *S pneumoniae* meningitis is critical. Despite implementation of a PCV-7 program in Alberta, rates of *S pneumoniae* meningitis in children <2 years of age is still high. Thus, continued research into safe and efficacious vaccines covering a broader range of *S pneumoniae* serotypes is necessary.

***STREPTOCOCCUS PNEUMONIAE* ALBERTA TEAM (SPAT) MEMBERS:** Stephanie Hui, Donna Hurteau, Marguerite Lovgren, Carol Mangan and Janice Pitchko.

ACKNOWLEDGEMENTS: The authors acknowledge the contributions of Carol Mangan, Stephanie Hui, Linda Hastie, and the efforts of the Data Collection Team – Anne Witschen, Lynne Korobanik, Freda Anderson, Loy Bacon, Shannon Pyra, Janine Schouten, Ambreen Mithani and Natalie Chui. They also thank Janice Pitchko for designing and maintaining the study databases and Heather Mangan for her assistance with the database, the staff of the Acute Diagnostic Microbiology Laboratories in Alberta who submitted isolates from cases of IPD to the National Centre

for Streptococcus, Edmonton, Alberta and the Provincial Laboratory for Public Health (Edmonton), The National Microbiology Laboratory, Winnipeg, Manitoba, and Wyeth Canada, Toronto, Ontario, for providing financial support for this work. Dr Johnstone receives salary support from the McMaster University Infectious Disease Bayer Healthcare Fellowship (2009–2010) and Canadian Thoracic Society (2010–2011).

FUNDING: This research was funded by a grant-in-aid from Pfizer Canada. The funder had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation, review or approval of the manuscript.

POTENTIAL CONFLICT OF INTERESTS: Dr Johnstone and Mrs Sipi Garg have no conflicts to report. Drs Tyrrell, Marrie and Kellner report that they have received unrestricted grant-in-aid support from Pfizer Canada for epidemiological studies of *S pneumoniae* infections, as well as compensation for consulting and speaking.

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