MAJOR ARTICLE

Changing Epidemiology of Invasive Pneumococcal Disease in Canada, 1998–2007: Update from the Calgary-Area *Streptococcus pneumoniae* Research (CASPER) Study

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(See the editorial commentary by Greenberg on pages 213–5)

Background. Routine infant vaccination with 7-valent pneumococcal conjugate vaccine (PCV7) began in the Calgary Health Region (Alberta, Canada) in 2002. We measured the impact of this vaccine program on invasive pneumococcal disease (IPD).

Methods. Prospective, population-based surveillance of all cases of IPD (with culture specimens obtained from sterile sites) was conducted from January 1998 through December 2007. Demographic and clinical data were collected. All viable isolates were saved and serotyped.

Results. There were 1182 IPD cases over the 10-year period. Comparison of the vaccine period (2003–2007) with the prevaccine period (1998–2001) revealed that the incidence of IPD due to PCV7 serotypes decreased significantly by 86%, 59%, 38%, and 78% in the 6–23-month, 2–4-year, 16–64-year, and 65–84-year age groups, respectively. The total number of IPD cases decreased by 77%, 45%, and 34% in the 6–23-month, 2–4-year, and 65–84-year age groups, respectively. The incidence of IPD due to non-PCV7 serotypes increased by 183%, and the total incidence of IPD increased by 73% among adults aged 16–64 years; however, this increase was primarily attributed to a large outbreak of serotype 5 IPD among homeless adults during the period 2005–2007. There were 5 cases of IPD due to PCV7 serotypes among vaccinated children in the vaccine period.

Conclusions. Since the introduction of PCV7 vaccine, there has been a profound decrease in the total number of cases of IPD among children and in cases due to PCV7 serotypes among subjects of all ages in Calgary, indicating a strong direct effect and herd effect of the vaccine. The serotypes that now cause IPD have changed significantly. The magnitude and impact of replacement IPD caused by non-PCV7 serotypes is not yet known.

The 7-valent pneumococcal conjugate vaccine (PCV7) was introduced for routine use in infants and high-risk children in the United States in 2000 [1]. It was subsequently introduced in Canada (in 2002) and many other countries. Numerous publications from the United States have described the direct effectiveness of PCV7 in vaccine recipients, as well as the indirect herd effect to prevent disease in unvaccinated children and adults [1–6].

We have conducted population-based surveillance for invasive pneumococcal disease (IPD) in Calgary, Alberta, Canada, since 1998, and we previously reported the early findings after introduction of routine 4-dose PCV7 vaccination for infants and high-risk children [7]. To the end of 2004 (after more than 2 full years of routine PCV7 use and compared with the period from 1998 to 2001), we found that IPD due to PCV7 serotypes had decreased by 93% among 6–23-month-old children and by 63% among 65–84-year-old adults [7]. To our knowledge, these was the first such data reported outside of the United States. There have now been pub-

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lished reports about the effectiveness of PCV7 for children in other Canadian provinces, in circumpolar regions (in the United States, Canada, and Norway), and other countries, including Australia and Spain [8–11].

More recently, reports about serotype replacement IPD and other diseases have come from the United States [5, 6, 12–14]. There are 91 known serotypes of the pneumococcus [15]. The 7 serotypes in PCV7 caused >80% of cases of IPD among children in the United States and Canada before the introduction of PCV7 [16, 17]. As the rate of disease caused by PCV7 serotypes decreases, the proportion of the remaining pneumococcal infections caused by nonvaccine serotypes will increase. This increase, or replacement, could be relative if the rate of nonvaccine serotype infections remains unchanged but the proportion of all pneumococcal infections caused by these nonvaccine serotypes increases. Alternatively, the replacement could be absolute if both the rate and the proportion of nonvaccine serotype infection increase. To address the issue of serotype replacement, new 10-valent and 13-valent protein-polysaccharide pneumococcal conjugate vaccines are in advanced stages of development [18].

We now report on continued surveillance of IPD in Calgary, Alberta, during the period 1998–2007 to describe trends in IPD rates and proportions of cases caused by PCV7 and non-PCV7 serotypes, as well as by serotypes within new experimental vaccines. We also report on cases of vaccine failure.

METHODS

The Calgary Area *Streptococcus pneumoniae* Epidemiology Research (CASPER) group began prospective population-based surveillance of IPD among persons of all ages in the Calgary Health Region (CHR) on 1 January 1998. Cases observed up to the date 31 December 2007 are reported here. The CHR includes the city of Calgary and several smaller surrounding communities. The study population included all persons who live within the boundaries of the CHR. Population estimates for each year were obtained from the CHR Department of Health Information Services and the Health Systems Analysis Unit. The population of the CHR increased from 888,432 persons in 1998 to 1,111,614 persons in 2007.

A case of IPD was defined as an acute illness in a person from whom pneumococcus had been isolated a normally sterile body site (e.g., blood, cerebrospinal fluid, synovial fluid, pericardial fluid, pleural fluid, lung tissue, or peritoneal fluid). Cases of IPD were identified through active, laboratory-based surveillance at the central microbiology laboratory (Calgary Laboratory Services) serving the entire CHR. Cases identified in persons living outside the CHR were excluded. Pneumococcus was identified using standard laboratory methods [19]. Serotype was determined on the basis of the Quellung reaction, with use of commercial antisera obtained from the Statens Seruminstitut (Copenhagen, Denmark); determination was performed at the National Centre for Streptococcus (Edmonton, Alberta, Canada).

Information on site of infection was obtained for all cases. Additional demographic information, medical history, immunization status, clinical presentation, course of illness, and outcome were obtained from retrospective chart reviews for all pediatric patients (age, <16 years) for 1998–2003 and for all adult patients for 2000–2003. Starting in mid-2003, a patient or family interview was conducted, and demographic and clinical information was collected concurrently.

Data was entered to a FileMaker Pro, version 9.0v3 (FileMaker), database and transferred to SPSS, version 16.0 (SPSS), or Stata/IC, version 10.0 (Stata Corporation), for analysis. Categorical data were summarized as proportions. Differences between groups were tested by Fisher's exact test for categorical variables.

The annual incidence of IPD disease was defined as the number of cases divided by the total CHR population during each year of the study and is expressed per 100,000 people for each of the following age groups: 0–5 months, 6–23 months, 2–4 years, 5–15 years, 16–64 years, 65–84 years, and ⩾85 years. Within each age group, rates were described for all cases, cases due to PCV7 serotypes, and cases due to non-PCV7 serotypes. Trend analysis was performed using Fisher's exact test to compare the period before the introduction of PCV7 (1998–2001) with the period of 5 full years after the introduction of PCV7 (2003–2007). We excluded 2002 (the year that PCV7 was introduced) from this analysis. In addition, we made single year comparisons between each of the years from 2003 to 2007 and the combined time period of 1998 to 2001.

A publicly funded PCV7 vaccination program began in the province of Alberta for all infants born 1 July 2002 and onwards, as well as for all high-risk children up to 5 years of age [20]. Routine vaccination with PCV7 is performed in public health clinics operated by the CHR, with all doses delivered by public health nurses. A 4-dose series is provided for infants, with doses given at 2, 4, 6, and 18 months of age [21]. An estimate of PCV7 vaccination rates in the CHR was made by counting the proportion of children born during the period from 1 July 2002 through 31 December 2006 who had received 3 doses of PCV7 by 12 months of age and 4 doses by 24 months of age. The proportion of children who had received 3 doses by the age of 12 months was 88%, 89%, 90%, 91%, and 91% for children born in 2002, 2003, 2004, 2005, and 2006, respectively. The proportion of children who received 4 doses by the age of 24 months was 74%, 81%, 86%, and 84% for children born in 2002, 2003, 2004, and 2005, respectively.

Since 1998, there has been an enhanced program in Alberta with the goal to deliver 23-valent plain polysaccharide pneumococcal vaccine (PPV23) to all persons aged ⩾65 years and

to all persons ⩾5 years with high-risk conditions. An accurate estimate of the proportion of eligible persons who have received PPV23 is not yet available.

The Conjoint Health Research Ethics Board of the University of Calgary and CHR approved this study. Written, informed consent was obtained for all interviews.

RESULTS

There were 1182 eligible cases of IPD during the period 1 January 1998 through 31 December 2007. Data on age and sex were obtained from all patients. Complete demographic and clinical data on the clinical course and outcome were obtained for 208 cases (99%) among children (age, <16 years) for the period 1998–2007 and for 810 cases (98%) among adults (age, ⩾16 years) for the period 2000–2007. Serotypes were determined for all 1173 viable isolates (99%).

The source of pneumococcal isolates (1 isolate per episode) included blood (89%), cerebrospinal fluid (5%), pleural fluid (4%), joint fluid (1%), and peritoneal fluid (1%). The most common disease states were pneumonia (75%), bacteremia (with or without sepsis syndrome or septic shock, 17%), and meningitis (6%) (figure 1).

For all cases combined, the 30-day case-fatality rate was 10%. By age group, the case-fatality rates were 0%, 1%, 6%, 0%, 8%, 20%, and 24% among patients aged 0–5 months, 6–23 months, 2–4 years, 5–15 years, 16–64 years, 65–84 years, and ⩾85 years, respectively.

Overall incidence and serotype-specific incidence of IPD. Table 1 presents the overall incidence of IPD, as well as the serotype-specific incidence, for all age groups for the time period before PCV7 introduction (1998–2001) versus the period after introduction (2003–2007). Table 2 presents the number of IPD cases caused by each serotype in each year, grouped by age and serotype group. By 2007, PCV7 serotypes were nearly eliminated, with only 1 and 10 cases among children and adults, respectively.

The tables show the impact of a large outbreak of 152 cases of serotype 5 IPD among adults in 2006 and 2007. The number of cases due to most other non-PCV7 serotypes was small, but statistically significant increases in the incidence of overall cases for the period 2003–2007, compared with the period 1998–2001, were found for serotypes 19A (from 0.1 to 0.3 cases per 100,000 person-years; $P = .021$) and 8 (from 0.3 to 1.1 cases per 100,000 person-years; $P < .001$). There was a nearly statistically significant increase in the incidence of IPD due to serotype 12F (from 0.2 to 0.4 cases per 100,000 person-years; $P = .062$).

Figures 2 and 3 illustrate the year-to-year trends for IPD overall, by PCV7 serotypes, and by non-PCV7 serotypes for children aged 0–23 months and adults aged 65–84 years. The incidence of IPD has been stable among young children since 2004 (figure 2), with a 94% decrease in IPD due to PCV7 serotypes and 79% decrease in overall cases of IPD in 2007, compared with the period 1998–2001. The baseline incidence

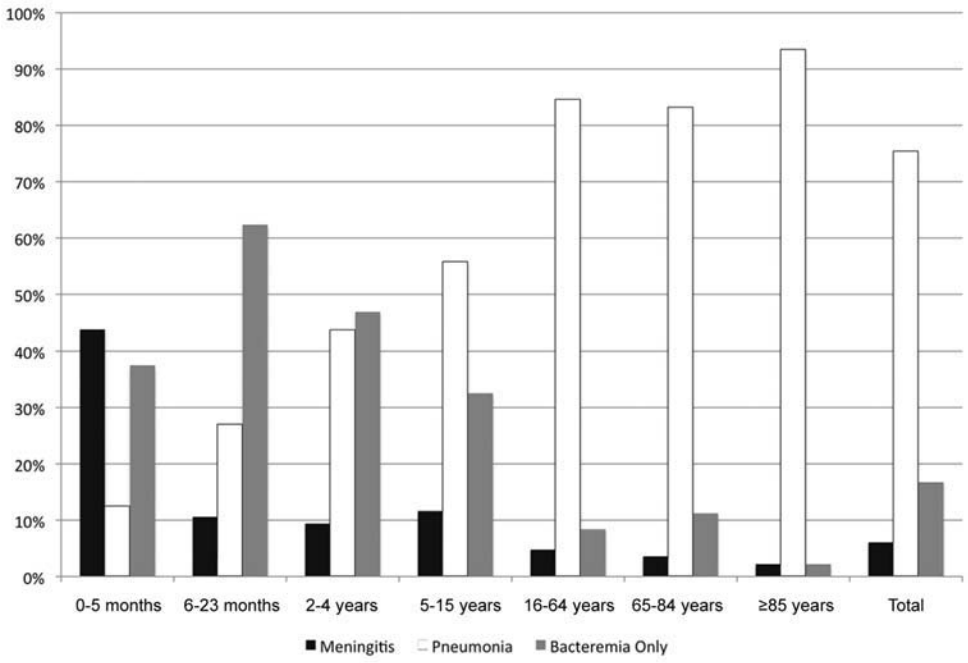

Figure 1. Primary invasive pneumococcal disease clinical presentation in Calgary, Alberta, Canada, by age, 1998–2007. All cases had positive results of culture of blood or other sterile site specimens. In total, 6% of cases involved meningitis, 75% involved pneumonia, and 17% involved bacteremia.

Table 1. Incidence of invasive pneumococcal disease in Calgary, Alberta, Canada, 1998–2001 (before the introduction of 7-valent pneumococcal conjugate vaccine [PCV7]) versus 2003–2007 (after the introduction of PCV7), by age group and serotype group.

Variable	Age group						
	0–5 months	6–23 months	2–4 years	5–15 years	16–64 years	65–84 years	⩾85 years
Total no. of cases							
1998–2001	5	55	33	19	182	108	17
2003–2007	8	18	24	18	456	104	32
Incidence, no of cases per 100,000 person-years							
All serotypes							
1998–2001	21.3	77.7	22.7	3.3	7.1	36.2	55.0
2003–2007	23.5	18.0	12.6	2.4	12.3	23.9	60.1
PCV7 serotypes							
1998–2001	12.8	66.4	17.9	2.5	3.6	22.1	29.1
2003–2007	5.9	9.0	7.3	1.3	2.2	4.8	22.5
Non-PCV7 serotypes							
1998–2001	8.5	11.3	4.8	0.7	3.5	14.1	25.9
2003–2007	17.7	8.0	5.2	1.1	10.0	18.8	35.7
Difference between 2003–2007 and 1998–2001							
All serotypes							
Change, %	+11	**−77**	**−45**	−27	**+73**[a]	**−34**	+9
P	>.99	<.001	.03	.41	<.001	.003	.88
PCV7 serotypes							
Change, %	−54	**−86**	**−59**	−45	**−38**	**−78**	−23
P	.41	<.001	.006	.15	.002	<.001	.65
Non-PCV7 serotypes							
Change, %	+107	−29	+8	+54	**+183**[a]	+34	+38
P	.49	.61	>.99	.57	<.001	.14	.55

NOTE. Statistical significance is denoted by boldface font.

[a] The overall increase in the 16–64-year-old age group was primarily related to an outbreak of invasive pneumococcal disease due to serotype 5 (see Results). If cases due to serotype 5 from 2005–2007 are excluded, the increase for all serotypes is 15% (from 7.1 to 8.2 cases per 100,000 person-years; $P = .14$), and the increase for non-PCV7 serotypes is 66% (from 3.5 to 5.8 cases per 100,000 person-years; $P < .001$).

of IPD during 1998–2001 also varied among adults (figure 3). Nevertheless, there has been a continued decrease in IPD due to PCV7 serotypes since 2002 and a gradual increase in IPD due to non-PCV7 serotypes. There has been no increase or decrease in IPD due to the serotypes contained in the 23-valent polysaccharide vaccine but not contained in PCV7 (data not shown).

IPD among vaccine-eligible children, 2003–2007. There were 66 cases of IPD among children aged <16 years during 2003–2007, and the serotype was known for 65 of the cases; 35 cases were caused by PCV7 serotypes, and 30 were caused by non-PCV7 serotypes. Of the 35 cases due to PCV7 serotypes, 3 occurred in children who were eligible to have received PCV7 but had not.

Five other cases occurred among children who had received ⩾1 dose of PCV7. Two of these children had received 3 doses of PCV7 by 6 months of age (serotype 14 meningitis and serotype 6B pneumonia), whereas the other 3 had received 1 dose (serotype 6B bacteremia, serotype 6B meningitis, and serotype 14 meningitis). Two of these children had significant underlying medical disorders (one had undergone liver transplantation, and the other had congenital arthrogryposis). The other 27 cases due to PCV7 serotypes occurred in children who were not eligible to have received PCV7.

DISCUSSION

This 10-year, population-based surveillance study determined that, after the introduction of universal 4-dose PCV7 infant vaccination in Calgary in 2002, there was a sustained decrease in the incidence of IPD due to PCV7 serotypes both among vaccine-eligible children and among older children and adults. We previously reported our initial observations after the first 2 full years of PCV7 use [7]. This report extends those observations, with increased statistical power and more complete clinical information. The large decrease in IPD due to PCV7 serotypes among vaccine-eligible children was expected on the basis of the clinical trials of PCV7 [22]. Data showing similar effectiveness have also been reported from the United States, Australia, Norway, and Spain [8–11], and reports from the

Table 2. Serotypes from 1173 viable invasive pneumococcal disease strains in Calgary, Alberta, Canada, 1998–2007, by age group and serotype group.

	No. of cases, by year and age group																			
	1998		1999		2000		2001		2002		2003		2004		2005		2006		2007	
Serotype	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults
PCV7 serotypes																				
4	2	14	1	9	0	14	3	16	1	6	0	8	0	8	0	2	0	11	1	6
6B	0	2	3	1	3	4	4	3	2	6	3	3	3	6	2	4	0	0	0	1
9V	0	4	2	3	0	8	2	2	3	1	0	6	0	2	0	3	3	2	0	1
14	10	15	9	13	4	11	11	12	10	10	6	9	1	2	1	5	2	1	0	0
18C	3	0	2	3	1	3	9	4	3	3	3	4	4	4	1	0	0	5	0	0
19F	0	4	2	4	7	4	2	2	4	3	3	2	0	1	2	2	0	3	0	1
23F	3	4	5	2	2	3	0	3	1	1	0	5	0	4	0	5	0	0	0	1
10-valent vaccine serotypes[a]																				
1	0	0	0	0	0	2	1	1	0	1	1	3	0	1	0	1	0	2	0	0
5	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	7	1	63	1	89
7F	0	4	0	3	0	2	2	1	0	2	0	5	0	3	0	4	0	0	2	2
13-valent vaccine serotypes[a]																				
3	0	6	1	7	0	4	2	8	0	10	0	8	2	2	1	11	1	7	2	4
6A	0	7	1	3	0	3	4	5	2	3	1	2	1	5	0	2	0	2	0	6
19A	0	1	0	0	0	0	2	0	0	0	0	2	0	4	0	0	1	2	2	6
Other serotypes																				
8	0	0	0	1	0	4	0	5	0	3	0	6	0	9	1	21	0	12	0	11
22F	0	3	0	10	0	2	1	4	1	7	0	4	0	3	1	9	2	8	1	11
9N	0	3	0	2	1	2	0	7	0	0	0	5	0	2	0	3	0	1	0	7
12F	0	1	0	1	0	1	0	4	0	1	0	3	0	3	0	6	0	8	0	3
11A	0	2	0	2	0	2	0	3	0	2	0	3	0	1	0	3	0	1	0	3
33F	0	1	0	0	0	2	1	2	0	2	0	2	0	1	0	0	0	1	0	1
16F	0	0	0	1	0	0	0	1	0	2	1	2	0	1	0	0	0	1	0	3
31	0	0	0	1	0	3	0	0	1	0	0	1	0	2	0	1	0	0	0	1
38	0	0	0	0	0	0	1	0	1	0	0	0	0	0	1	2	0	1	0	4
Other[b]	0	1	1	2	1	5	2	4	2	7	0	6	2	11	2	10	2	15	3	14
Total	18	72	27	68	19	79	47	88	31	71	18	89	13	75	12	101	12	146	12	175

NOTE. Children were aged <16 years, and adults were aged ⩾16 years. PCV7, 7-valent pneumococcal conjugate vaccine.

[a] Ten-valent vaccine serotypes include all serotypes in PCV7 plus serotypes 1, 5, and 7F; 13-valent vaccine serotypes include all serotypes in the 10-valent vaccine plus serotypes 3, 6A, and 19A.

[b] Other serotypes include 35B ($n = 9$), 34 ($n = 8$), 17F ($n = 7$), 10A ($n = 6$), 23A ($n = 6$), 15B ($n = 5$), 33A ($n = 5$), 35F ($n = 5$), 11B ($n = 4$), 15A ($n = 4$), 9L ($n = 4$), 15C ($n = 3$), 18B ($n = 3$), 20 ($n = 3$), 10F ($n = 2$), 23B ($n = 2$), 7C ($n = 1$), 11C ($n = 1$), 11F ($n = 1$), 12A ($n = 1$), 13 ($n = 1$), 21 ($n = 1$), 28A ($n = 1$), 29 ($n = 1$), and 35A ($n = 1$); 5 were nontypeable.

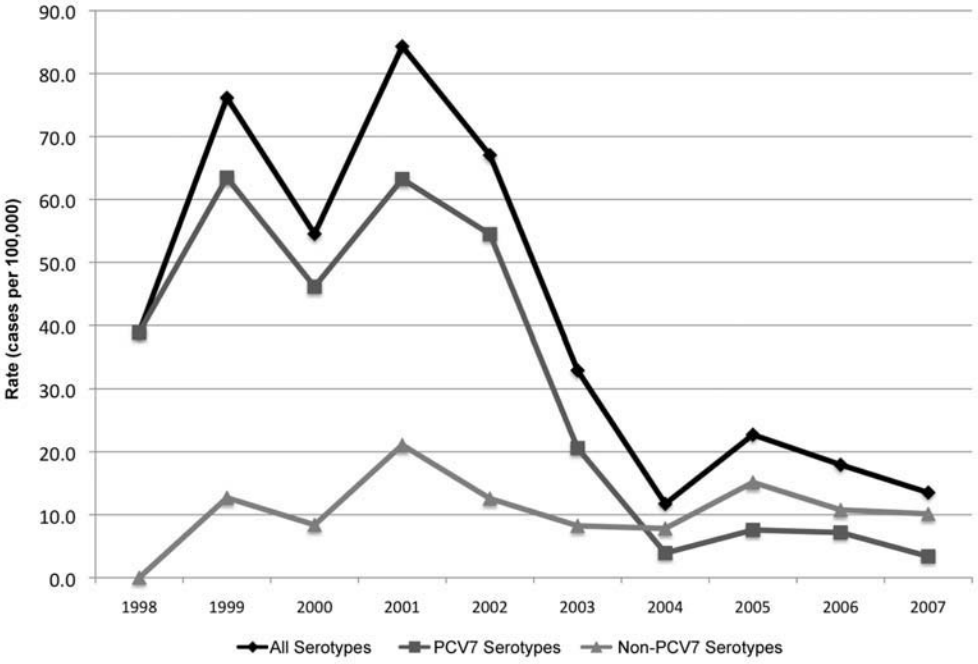

Figure 2. Incidence of invasive pneumococcal disease in Calgary, Alberta, Canada, by serotype grouping, for children aged 0–23 months, 1998–2007. For 2007 vs. 1998−2001, there was a −79% change in the incidence for all serotypes ($P < .001$), a −94% change for 7-valent pneumococcal conjugate vaccine (PCV7) serotypes ($P < .001$), and a +139% change for non-PCV7 serotypes ($P = .37$).

United States have shown a similar sustained decrease in IPD due to PCV7 serotypes [6].

A related finding of this study is the observation of sustained decreases in PCV7 serotype–associated IPD among adults, suggesting that there is a herd effect associated with vaccination of young children, leading to reduced asymptomatic nasopharyngeal colonization of vaccine recipients and reduced transmission of PCV7 serotype strains to unvaccinated persons [23].

Observational studies cannot prove a cause-and-effect relationship between variables, such as whether PCV7 vaccination caused a herd effect to prevent IPD in those who were not vaccinated. However, criteria such as those by Hill [24] indicate whether causal relationships can be inferred. Most of Hill's criteria are applicable to our data, including biologic plausibility and coherence, strong statistical association, temporal relationship, supportive evidence from experimental clinical trials, and consistent or analogous observations made by others. Additional supportive evidence, reported by ourselves and others, has demonstrated that PCV7 vaccination has both a direct effect and a herd effect to prevent nasopharyngeal colonization with PCV7 serotypes, and colonization always precedes pneumococcal disease [25].

In contrast, over the same time period, we observed a significant increase in the incidence of IPD due to non-PCV7 serotypes among persons aged 16–64 years, with nonsignificant trends for other age groups, suggesting that serotype replacement with non-PCV7 vaccine serotypes reduces the benefits of PCV7 vaccination. However, the findings for this age group were skewed by a large outbreak of IPD due to serotype 5, primarily during the years 2006 and 2007, when this single serotype was responsible for 47% of all cases of IPD. Preliminary details of this outbreak, which was caused by a single genetic multilocus sequence typing strain and which predominantly affected homeless, middle-aged illicit drug users, have been reported elsewhere, and a complete report is in preparation [26]. When the cases due to serotype 5 were excluded from analysis, there was no longer an increase in the overall incidence of IPD among persons aged 16–64 years, although there was still a statistically significant increase in the incidence of cases due to all other non-PCV7 serotypes combined, including statistically significant individual increases for serotypes 8 and 19A.

It is not known whether the use of PCV7 vaccine somehow caused the outbreak of IPD due to serotype 5. However, again in reference to Hill's criteria [24], it is not clear how this could be so. First, although there was a temporal relationship, outbreaks of IPD have been known to occur long before the introduction of PCV7 [27, 28]. Second, it is not biologically plausible that a single strain of non-PCV7 pneumococcus would preferentially and temporarily cause disease in only one part of the population if it was replacing formerly endemic strains.

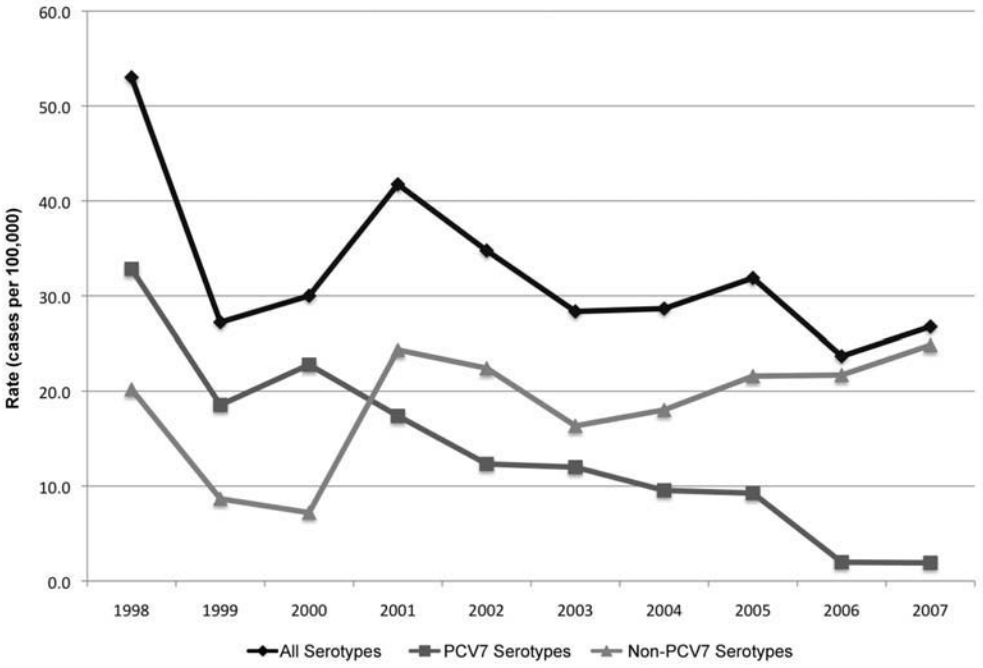

Figure 3. Incidence of invasive pneumococcal disease in Calgary, Alberta, Canada, by serotype grouping, for persons aged ⩾65 years, 1998–2007. For 2007 vs. 1998–2001, there was a −29% change in the incidence for all serotypes ($P = .11$), a −92% change for 7-valent pneumococcal conjugate vaccine (PCV7) serotypes ($P < .001$), and a +64% change for non-PCV7 serotypes ($P = .04$).

Regardless, the issue of replacement disease with non-PCV7 serotypes is an important one that continues to evolve. In the United States, replacement disease has been primarily reported among adults and, in particular, in small populations (e.g., Alaskan Aboriginal children from certain regions of the state) [14]. It is not yet clear whether the incidence of replacement-serotype IPD cases is increasing or leveling off. Data from the Active Bacterial Core surveillance program in the United States indicate that the ratio of IPD cases due to PCV7 serotypes among children aged <5 years that were prevented, compared with the increase in cases due to non-PCV7 serotypes in the same age group, was 21:1 in 2003, but this ratio dropped to 12:1 in 2005 [5, 6].

As the proportion of IPD cases caused by PCV7 serotypes continues to decrease, serotype epidemiology of IPD is changing profoundly, and reports of serotype distribution from before the implementation of PCV7 are no longer relevant in regions where PCV7 is used. This study found a large decrease in the proportion of IPD cases caused by PCV7 serotypes during 2003–2007, compared with 1998–2001, among both children and adults. Two experimental 10-valent and 13-valent protein-polysaccharide pneumococcal conjugate vaccines are in advanced stages of development, both of which cover a larger proportion of the serotypes that caused IPD during 2003–2007 in children and adults. The 13-valent vaccine, not surprisingly, has better coverage than the 10-valent vaccine.

There were very few vaccine failures in our study. Two children had received 3 doses of PCV7 by 6 months of age before they developed IPD due to a PCV7 serotype when they were >15 months of age. The 4-dose schedule for PCV7 in the province of Alberta involves administration age 2, 4, 6, and 18 months of age. One study found little difference in prebooster antibody levels between children who received booster doses at 15 months versus those who received them at 18 months [21]. Nonetheless, these 2 cases raise a concern that the gap between the primary series and the booster dose may be too long, at least for some children. To address this, a more relevant measure would be the incidence of vaccine failure in children aged 6–11 months versus that in children aged 12–17 months, but data about the per-month age group–specific vaccination status were not available. However, on the basis of the available estimates of vaccine coverage in Calgary, it is notable that the proportion of children aged 12 and 24 months who had received 4 doses of PCV7 increased to 91% and 84%, respectively, by the end of 2007. So, although there was a sizable minority of children who had received just 3 doses, vaccine failures among these children were rare.

The main limitation of these data is the relatively small number of IPD cases each year measured in just 1 city and surrounding region. As a result, there was more year-to-year variation in the incidence of IPD in some serotype groupings. However, the duration of our study before and after the in-

troduction of PCV7 makes it possible to determine longer-term trends.

In sum, IPD remains an important clinical problem in our region. Since the introduction of PCV7 vaccine, there has been a profound decrease in the overall incidence of IPD among children and in PCV7 serotype–associated IPD at all ages. The magnitude and impact of replacement IPD caused by non-PCV7 serotypes is not yet known. The serotypes that cause IPD have changed significantly, but newer, expanded valency conjugate vaccines could improve the coverage against these serotypes. Ultimately, the ideal vaccine against the pneumococcus will have universal coverage against all serotypes.

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