

# ANALYSIS

## Progress in the prevention of pneumococcal infection

**S***treptococcus pneumoniae* (pneumococcus) remains an important human pathogen more than a century after its discovery, with infections occurring most commonly among young children and elderly people. It causes a wide range of invasive infections in normally sterile body sites such as blood and cerebrospinal fluid (e.g., bacteremic pneumonia, meningitis), and noninvasive infections in nonsterile body sites such as middle ear fluid (e.g., otitis media).

Until recently, the only vaccine for pneumococcal infections was the 23-valent polysaccharide vaccine (PPV23), which is active against the 23 most common of 90 known capsular polysaccharide serotypes. This vaccine is moderately effective in preventing invasive infections in adults but does not prevent noninvasive infections such as nonbacteremic pneumonia.<sup>1</sup> PPV23 is not effective in young children because the polysaccharide antigens induce T-cell independent immunity, which leads to low antibody levels and poor immunologic memory. By 2000 all provinces and territories had implemented programs to vaccinate all people 65 years and older as well as younger adults with high-risk conditions. Uptake has been low.

A 7-valent protein-polysaccharide conjugate vaccine (PCV7) was developed for use in children. The 7 serotypes, all of which are also in PPV23, cause most of the pneumococcal infections in children. Conjugate vaccines induce T-cell dependent immunity in young children, which leads to effective antibody production and immunologic memory. Clinical trials have shown that PCV7 is highly efficacious in preventing invasive infections, with lower efficacy against pneumonia and otitis media. The vaccine was licensed in the United States in 2000.

## The results of a large effectiveness study showed sharp reductions in the number of invasive infections among children.

The results of a large effectiveness study showed sharp reductions in the number of invasive infections among vaccine-eligible children by the end of 2001. There were also significant reductions among older children and adults, which suggested an indirect benefit from herd immunity through reduced transmission of vaccine serotype strains from children (the largest natural reservoir of pneumococcus) to adults.<sup>2</sup> The decline in overall infection (regardless of serotype) was 69% for those younger than 2 years, 59% for those younger than 5 years, 32% for those 20–39 years and 18% for those older than 64 years.<sup>2</sup>

In 2001 PCV7 was licensed in Canada, and, in early 2002, the National Advisory Committee on Immunization recommended routine vaccination of all unvaccinated healthy children up to 59 months of age with a 4-dose schedule (Table 1). Because of the vaccine's high cost, publicly funded PCV7 programs were not immediately implemented. Alberta and Nunavut were the first jurisdic-

tions to implement routine PCV7 vaccination programs, in September 2002. No province or territory currently funds provision of a single dose of PCV7 to previously unvaccinated healthy children 24–59 months of age.

The Calgary Area *Streptococcus pneumoniae* Epidemiology Research (CASPER) team conducts prospective population-based surveillance of all cases of invasive *S. pneumoniae* infection occurring in the Calgary Health Region, whose population now exceeds 1 million. Data collected from 1998 to 2004 illustrates the impact of both pneumococcal vaccines.

We identified cases of invasive *S. pneumoniae* infection in patients with an acute illness and in whom *S. pneumoniae* was isolated from one or more normally sterile body sites. Cases were identified through active laboratory-based surveillance at the central microbiology laboratory. We estimated vaccination coverage with PCV7 for children born after June 2002. For adults 65 years and older we estimated vaccina-

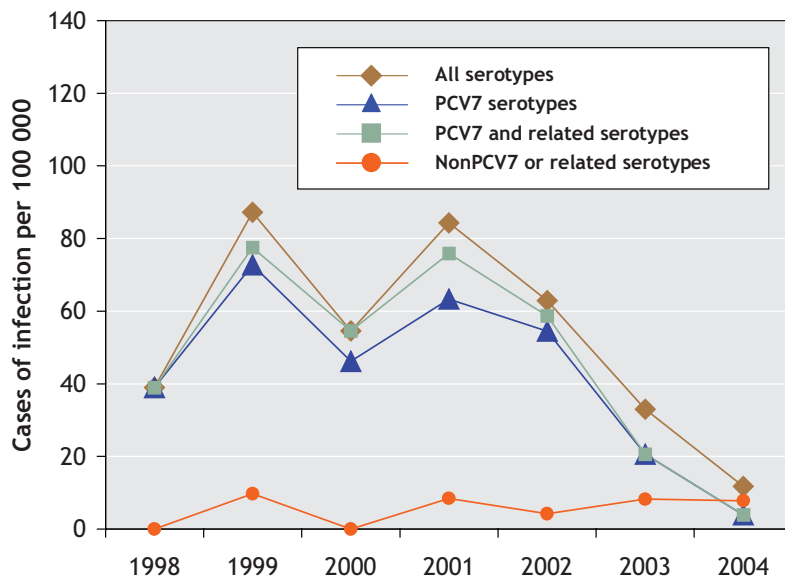
**Table 1:** National Advisory Committee on Immunization recommended PCV7 vaccine schedule for previously unvaccinated healthy children

Age at first dose, mo	Primary series*	Booster dose†
2-6	3 doses, 8 wk apart‡	1 dose at 12-15 mo
7-11	2 doses, 8 wk apart‡	1 dose at 12-15 mo
12-23	2 doses, 8 wk apart	None
24-59	1 dose	None

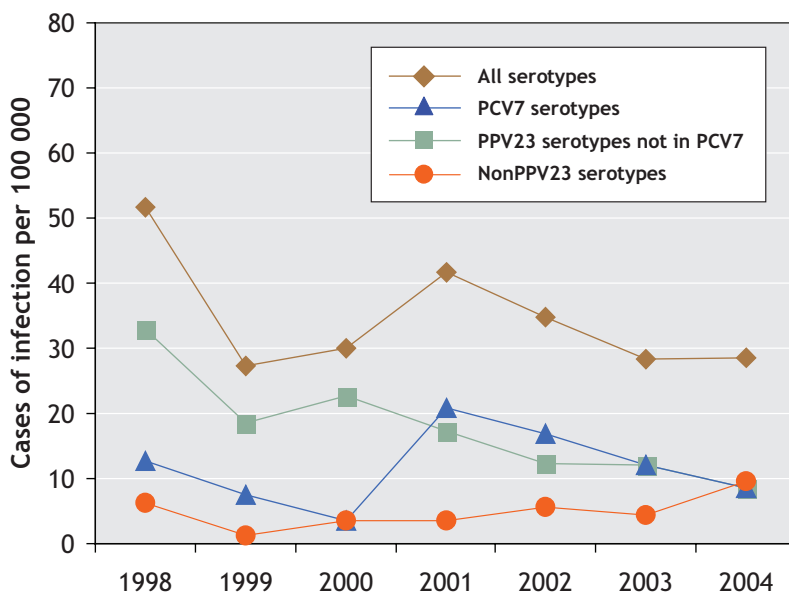
\*The vaccine can be administered simultaneously with other routine vaccinations at a separate site at the same visit.

†Booster doses are to be given at least 6-8 weeks after the final dose of the primary series.

‡For children vaccinated at < 1 year of age, the minimum interval between doses is 4 weeks.



**Fig. 1:** Cases of invasive pneumococcal infection per 100 000 among children 23 months of age and younger according to year and serotype group. Data from CASPER Surveillance, 1998–2004 ( $\chi^2$  or Fisher exact test for comparisons). When compared with the combined rate between 1998 and 2001, the rate in 2004 decreased by 81.6% to 11.7 (95% confidence interval [CI] 2.4–34.3) for all serotypes ( $p = 0.02$ ), by 92.6% to 3.9 (95% CI 0.1–21.8) for PCV7 serotypes ( $p < 0.001$ ) and by 93.4% to 3.9 (95% CI 0.1–21.8) for PCV7 and related serotypes within the same serogroups ( $p < 0.001$ ). There was no significant rate change for non-PCV7 or related serotypes ( $p = 0.61$ ).



**Fig. 2:** Cases of invasive pneumococcal infection per 100 000 among adults 65 years and older according to year and serotype group. Data from CASPER Surveillance, 1998–2004 ( $\chi^2$  or Fisher exact test for comparisons). When compared with the combined rate between 1998 and 2001, the rate in 2004 decreased by 62.7% to 8.5 (95% CI 3.7–16.7) for PCV7 serotypes ( $p = 0.007$ ); the change of 23.9% to 28.6 (95% CI 18.9–41.7) for all serotypes was not significant ( $p = 0.24$ ), nor was the change of 24.1% to 8.5 (95% CI 3.7–16.7) for PPV23 serotypes that are not in PCV7 ( $p = 0.59$ ). The increase of 163.9% to 9.5 (95% CI 4.4–18.1) for non-PPV23 serotypes was significant ( $p = 0.03$ ).

tion status with PPV23 since 1998. We defined the incidence rate as the number of cases over the total Calgary Health Region population during each year of the study. The Conjoint Health Research Ethics Board of the University of Calgary and Calgary Health Region approved the study.

There were 714 cases of invasive *S. pneumoniae* infection between 1998 and 2004. The most common diagnoses (not mutually exclusive) were bacteremia or sepsis (97.5%), pneumonia (70.0%) and meningitis (6.6%). The case-mortality rate was higher among adults (13.3% of cases  $\geq 16$  years v. 2.3% of cases  $< 16$  years,  $p < 0.001$ ).

The figures show the 7-year trends. Among children up to 23 months of age, the introduction of PCV7 in 2001 was followed by significant declines in the number of cases caused by PCV7 and related serotypes with no increase in those caused by serotypes not related to PCV7 (Fig. 1). Among adults 65 years and older (Fig. 2), a significant decline in the number of cases caused by PCV7 serotypes was accompanied by an increase in the number caused by serotypes not in PPV23.

By December 2004, it was estimated that 73.7% of children born between July and December 2002 had received 4 doses of PCV7. Another 14.6% had received 3 doses. The estimated cumulative proportions of adults 65 years and older who had been vaccinated with PPV23 was just 3.7% in 1998 and then increased gradually from 41.3% in 1999 to 59.2% in 2004.

The introduction of universal PCV7 immunization for infants in Calgary led to a prompt and large decline in the incidence of invasive infection among children under 2 years of age. There has also been a decline in the incidence of PCV7-serotype invasive *S. pneumoniae* infection among adults 65 years and older.

As in the United States, the magnitude of the decline among older people is likely due to the indirect effect of PCV7 rather than a direct effect of PPV23 because the reduction among adults over 65 years was only for infections caused by PCV7 serotypes and was larger than any reduction expected from the use of PPV23.<sup>3</sup>

There has been a report from the United States of an increased rate of invasive pneumococcal infection caused by non-PCV7 serotypes, particularly among adults, although the number of cases is small compared with the much larger decrease in PCV7-serotype cases at all ages.<sup>4</sup> This serotype replacement is not surprising with the use of serotype-based vaccines that prevent some but not all pneumococcal infections. However, it is not known how large this effect will eventually become. The smaller population and shorter term of surveillance in our study has not yet detected definite serotype replacement, but observations such as the increase in non-PPV23-serotype cases in 2004 need continued scrutiny.

There is no doubt that the vaccination of young children with PCV7 and adults with PPV23 will prevent illness, hospital admissions and death due to infection. Ongoing surveillance is needed to determine the long-term direct and indirect effects of PCV7 and PPV23 in the prevention of pneumococcal infection.

**James D. Kellner**

Professor  
Department of Pediatrics  
University of Calgary

**Deirdre L. Church**

Professor  
Department of Pathology and  
Laboratory Medicine  
University of Calgary

**Judy MacDonald**

Deputy Medical Officer of Health  
Calgary Health Region  
Calgary, Alta.

**Gregory J. Tyrrell**

Director  
National Centre for Streptococcus  
Edmonton, Alta.

**David Scheifele**

Professor  
Department of Pediatrics  
University of British Columbia  
Vancouver, BC

This article has been peer reviewed.

**Competing interests:** None declared for Judy MacDonald or Greg Tyrell. James Kellner has received an unrestricted, investigator-initiated research grant from Wyeth Canada, which supported the surveillance study. David Scheifele is the recipient of the Canadian Institute for Health Research/Wyeth Chair in Clinical Vaccine Research.

**Acknowledgements:** Funding for CASPER was obtained from the Alberta Children's Hospital Foundation and an unrestricted grant from Wyeth Canada. We thank the study staff and associates including Linda Hastie, Stephanie Hui, Janice Pitchko and Heather Semeniuk for their many contributions.

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