Lack of impact of infant PCV vaccination on rates of adult invasive pneumococcal disease in Ontario, Canada

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Abstract (updated)

BACKGROUND: Use of conjugate pneumococcal vaccine is changing the epidemiology of invasive pneumococcal disease (IPD) in adults. We report the results of surveillance for adult IPD in Toronto and Peel regions, Ontario, Canada in the first 10 years after the 2001 licensure of the 7-valent pneumococcal conjugate (PCV7) in children.
METHODS: Population-based surveillance for IPD has been performed in Toronto and Peel region (pop'n 4M) since 1995. Serotyping and antimicrobial susceptibility testing are performed in a central study laboratory.
RESULTS: Between 1996/97 and 2002/03 the rate of adult IPD declined from 10.8 to 8.1 per/100,000/yr and has since remained stable. A similar pattern was observed in all age categories (Table1).

Table 1. Adult IPD cases per 100,000 population, 1996-2011

	1996/97	1998/99	2000/01	2002/03	2004/05	2006/07	2008/09	2010/11
Age groups								
15-44 years	4.6	4.2	3.6	3.2	3.3	2.9	3.0	2.2
45-64 years	11.5	11.0	10.7	8.2	9.3	8.3	9.1	8.5
65-74 years	30.6	26.3	18.4	23.6	19.3	21.1	16.5	17.4
75+ years	77.5	61.6	53.2	41.6	28.7	32.1	34.8	28.7
All adults	12.8	11.3	9.8	8.7	8.0	7.9	8.2	7.3

Disease due to PCV7 serotypes (ST) decreased significantly in all age groups. IPD caused by non-PCV7 serotypes significantly increased. The extent of changes in IPD caused by vaccine-covered serotypes differed among age groups. Between 2000/01 and 2010/11, PCV13/not PCV7 increased significantly in all adults except those aged +75 yrs. Between 2000/01 and 2004/05, IPD caused by serotypes included in PPV23/not PCV doubled in adults 15-44 and 65-74 yrs, then decreased. In adults +75 yrs, PPV23 has decreased since 2000/02. Non-vaccine STs began to increase in all age groups after 2004/05.
Resistance to erythromycin and beta-lactam antibiotics increased in all age groups between 2001 and 2011. Resistance to fluoroquinolones and TMP-SMX did not change.
CONCLUSIONS: Although routine infant PCV7 vaccination programs have been associated with substantial declines in PCV7 STs adult IPD, the seroepidmiology of adult IPD is complex. Overall adult IPD rates have not changed since 2003. Antibiotic resistance has increased.

Background

From 1995 to 2011, prospective, population-based surveillance for invasive pneumococcal disease (defined as illness associated with a sterile site isolate of *S. pneumoniae*) has been conducted in metropolitan Toronto and Peel region (population 4.1 million in 2011) Ontario, Canada. Adult PPV23 vaccination was introduced over a 2-year period in 1995/96 for adults 65 years or greater and those between 2 and 64 yrs old who had an underlying chronic illness as defined identified by the National Advisory Committee on Immunization, Canada. PCV7 vaccine was licensed and available for purchase for individual use in June 2001 and a publicly-funded infant PCV7 vaccination program began in January 2005.

Methods

Each case of IPD identified in laboratories servicing the population surveillance area is reported to a central study office at Mount Sinai Hospital. Demographic and clinical data are collected on each case of IPD from review of health records and interviews with patients and attending physicians. Population data are obtained from Statistics Canada. Antimicrobial susceptibility testing is performed at the central study laboratory by broth microdilution and interpreted to CLSI standards. Serotypes are determined using latex pneumococcal antisera (Statens Serum Institute, DK) and the Quellung reaction

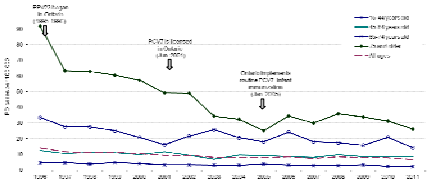
Statistical analysis was performed using SAS (version 9.2). Serotype-specific incidence was calculated accounting for missing isolates, assuming that distribution of serotypes for cases with missing values were the same as the distribution for cases with available results. Rates were assessed as relative risk between two time points and reported as percentage change.

Results

From 1995 to 2011, 4,838 cases of adult (>=15 yrs) IPD were identified. 4,362 (90.2%) of isolates were available for antimicrobial susceptibility testing and serotyping. The mean patient age was 62.6 yrs (range 15-108) and 2,622 (54.2%) were males. 3,200 (66.2%) had an underlying chronic illness, 268 (5.5%) were HIV positive, and 863 (17.8%) had some other immunocompromising condition.

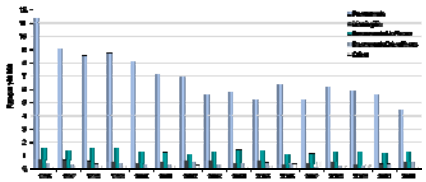
There was a 38% reduction in the rate of adult IPD between 1996/97 and 2004/05 from 12.8 to 8.0 cases per 100,000 pop'n (p <.0001). In this period, the decline was from 4.6 to 3.3 cases/100,000 in adults 15-44 yrs (28% reduction, p=0.06), from 11.5 to 9.3 cases/100,000 pop'n in adults 45-64 yrs (19%, p=0.19), from 30.6 to 19.3 cases/100,000 pop'n in persons 65-74 yrs (37%, p=0.01), and from 77.5 to 28.7 cases/100, 000 pop'n in adults 75+ yrs (63%, p<0.0001). Between 2004/05 and 2010/11, adult IPD incidence did not change significantly overall; IPD incidence remained relatively stable at 8.0 cases per 100,000 pop'n (Table 1, Figure 1) (overall decrease by 8%, p=0.33).

Figure 1. Adult IPD cases per 100,000 population by age groups, 1996-2011



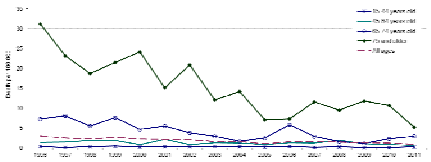
The incidence of invasive pneumonia declined from 11.3 to 4.5 cases/100,000 pop'n between 1996 and 2011. Rates of meningitis and bacteremia without focus did not change (Figure 2), remaining at 0.5/100,000 pop'n and 1.3 cases/100,000 pop'n, respectively.

Figure 2. Adult IPD cases per 100,000 population by disease syndrome, 1996-2011



The overall case fatality rate (defined as death within 30 days of positive culture) was 20%. Case fatality was 8.8%, 14.1%, 18.5%, 34.0% in age groups 15-44, 45-64, 65-74, and 75 + years old, respectively. Between 1996/97 and 2004/05 there was a 51% reduction in overall rate of death in adults following episodes of IPD from 2.9 to 1.3 deaths per 100,000 pop'n (p=<0.0001) (Figure 3) with a significant reduction in adults >=65 yrs (15.5 to 6.1 deaths/100,000 pop'n, p=<0.0001). A modest decrease of 17% (1.2 to 1.0 deaths/100,000 pop'n, p=0.40) has been observed since 2004/05.

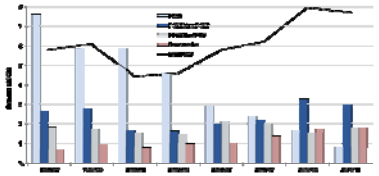
Figure 3. IPD associated deaths per 100,000 population by age groups, 1996-2011



Results (con't)

Between 2000/01 and 2010/11, adult IPD due to PCV7 serotypes decreased from 5.9 to 0.8 cases/100,000 pop'n, a reduction of 86% (p<0001), while disease due to non-PCV7 serotypes increased by 71% from 4.5 to 7.7 cases/100,000 pop'n (p<0001) (Figure 4). Adult IPD due to PCV13/not PCV7 serotypes increased from 1.6 to 3.0 cases/100,000 pop'n (p=0.001). Adult IPD due to non-vaccine serotypes continues to increase while IPD caused by serotypes included in PPV23 but not in PCV13 has not changed.

Figure 4. Adult IPD cases per 100,000 population by vaccine serotype groups, 1996-2011



IPD due to PCV7 serotypes decreased significantly in all age groups (Figure 5a). Changes in IPD caused by vaccine-covered serotypes differed among age groups (Figure 5b-5d). Between 2000/01 and 2010/11, IPD due to PCV13/not PCV7 increased in all adults except those aged +75 yrs (6% reduction in those +75 yrs, p=0.83). In adults 45-64 and 65-74 yrs, rates increased by 129% (p=0.02) from 1.4 to 3.2 cases/100,000 pop'n and 228% (p=0.006) from 2.5 to 8.2 cases/100,000 pop'n, respectively (Figure 5b).

Figure 5. Adult IPD cases per 100,000 pop'n by age and vaccine serotype groups, 1996-2011

Figure 5a. IPD caused by PCV7 serotypes

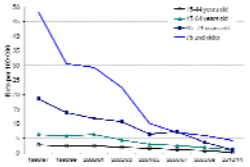
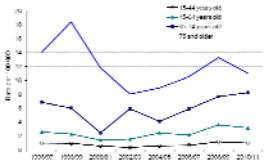


Figure 5b. IPD caused by PCV13/not PCV7 serotypes



Between 2000/01 and 2004/05, IPD caused by serotypes included in PPV23/not PCV increased notably in adults 15-44 and 65-74 yrs (Figure 5c); rates increased from 0.4 to 0.8 cases/100,000 pop'n (increase 100%, p=0.12) and from 2.6 to 5.5/100,000 pop'n (112%, p=0.12), respectively. This was followed by a decrease over the next five years (non-significant). In adults +75 yrs, IPD due to PPV23/not PCV serotypes decreased between 2001 and 2011 (42%, p=0.20).

From 2000/01 to 2010/11, IPD due to non-vaccine serotypes (Figure 5d) increased significantly by 183% (p=0.03) in adults 45-64 yrs from 0.6 to 1.7 cases/100,000 pop'n. In adults +75 yrs, IPD rates increased between 2005/06 and 2010/11 by 280% (p=0.003) from 2.5 to 9.5 cases/100,000 pop'n (Figure 5d).

Figure 5c. IPD caused by PPV23/not PCV serotypes

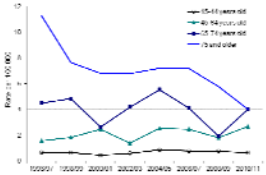
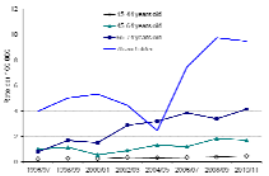


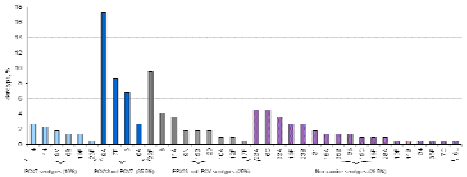
Figure 5d. IPD caused by non-vaccine serotypes



Results (con't)

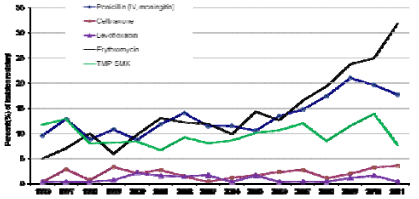
By 2011, serotypes covered by PCV7 vaccine accounted for 10% of all adult IPD, while serotypes included in PCV13/not PCV7, PPV23/not PCV serotypes and non-vaccine serotypes were responsible for 35.5%, 25.0% and 29.5% of disease, respectively. Distribution of individual serotypes is presented in Figure 6.

Figure 6. Serotypes distribution for adult IPD cases, 2011



Since 2001, resistance to penicillin, ceftriaxone and erythromycin has increased in all age groups, while resistance to levofloxacin and TMP-SMX remained stable (Figure 7). Resistance to penicillin and erythromycin increased in all vaccine-covered serotype groups (data not shown). Resistance to ceftriaxone increased only in serotypes included in PCV13 (data not shown).

Figure 7. Percent of isolates resistant to antibiotics, adult IPD cases, 1996-2011



Conclusions

- Childhood PCV7 vaccination resulted in a significant decline of IPD due to PCV7 serotypes in adults of all ages, suggestive of herd immunity effects. However, the decrease in rate of IPD due to PCV7 serotypes was replaced by an increase in rates of IPD caused non-PCV7 serotypes. Overall, adult IPD rates have not changed significantly since the introduction of childhood vaccination with PCV7.
- As of 2011, non-PCV serotypes constitute >50% of burden of IPD in adults, among which non-vaccine serotypes account for nearly 30% of all adult IPD cases.
- Changes in IPD caused by non-PCV7 serotypes differ among age groups.
- There remains a need to carefully monitor emergence of non-PCV serotypes and their effects on severity of disease and mortality associated with IPD.
- Assessment of PPV23 vaccination effectiveness in the context of childhood PCV programs would help to inform vaccination recommendations for adults.

Acknowledgements

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