What will Happen to Antimicrobial Resistance in Adult Invasive Pneumococcal Disease after the Introduction of Infant PCV13 Vaccination in Canada?

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CBSN Canadian Bacterial Surveillance Network

MOUNT SINAI HOSPITAL

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Abstract (Updated)

Background:
Infant PCV13 vaccination will likely affect both serotype (ST) distribution and antibiotic resistance in adult pneumococcal infections. The Canadian Bacterial Surveillance Network (CBSN) has been monitoring trends in antimicrobial resistance in Canadian pneumococci since 1993 and in ST distribution since 2000. We analyzed trends in antimicrobial resistance in pneumococcal serotypes (STs) included in PCV13 and other STs causing disease in Canadian adults.

Methods:
CBSN is a collaborative network of Canadian microbiology laboratories from 11 provinces and territories that systematically samples pneumococci for broth microdilution susceptibility testing performed to CLSI standards. Since 2000, all sterile site isolates (SSI) have been serotyped.

Results:
Of 10,305 SSI submitted from 2000–2011, 8,077 (79%) were from adults and 6,951(68%) were PCV13 STs. Antimicrobial susceptibility in PCV13 and non-PCV13 STs from adult SSI are shown in Table 1 as percent resistant (R) (non-meningeal breakpoints for amoxicillin and ceftriaxone resistance, oral penicillin breakpoints used).

Table 1. Trends in antimicrobial resistance in pneumococcal disease, Canada, 2000–2011

Year		2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Total Number of Isolates Tested	N	683	639	697	625	702	722	681	659	724	637	678	576
Percent (%) Pen V R*	Overall	4.3	4.9	5.5	4.8	3.1	4.3	4.4	2.7	3.9	5.5	4.7	5.0
	PCV13	5.0	6.2	7.1	5.7	4.4	6.1	6.0	4.5	5.7	6.7	7.8	7.3
	non-PCV13	2.3	1.2	1.1	2.7	0.5	1.2	1.6	0.0	1.6	3.4	1.0	2.8
Percent (%) Amox R**	Overall	0.0	0.6	0.6	1.0	0.1	1.0	0.7	0.8	0.8	1.7	1.8	2.4
	PCV13	0.0	0.9	0.8	1.4	0.2	1.5	1.2	1.2	1.5	3.0	3.2	4.9
	non-PCV13	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Percent (%) of Ctx R**	Overall	0.0	0.1	0.0	0.3	0.0	0.0	0.3	0.0	0.0	0.0	0.6	0.2
	PCV13	0.0	0.2	0.0	0.5	0.0	0.0	0.5	0.0	0.0	0.0	1.1	0.4
	non-PCV13	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Percent (%) of Ery R	Overall	9.2	11.0	10.0	12.4	14.3	16.5	14.5	18.5	19.1	21.0	26.1	29.0
	PCV13	9.3	12.5	11.0	15.7	16.0	20.1	17.5	22.4	18.7	23.1	27.5	31.5
	non-PCV13	9.0	6.9	7.5	4.8	10.4	10.0	9.4	12.5	19.5	18.1	24.3	26.6
Percent (%) of Levo R	Overall	1.2	0.8	1.6	0.6	0.7	1.3	0.4	0.5	0.6	0.8	0.9	0.9
	PCV13	1.4	0.6	1.2	0.5	0.4	1.3	0.7	0.5	0.7	1.3	1.1	0.4
	non-PCV13	0.6	1.2	2.7	1.1	1.4	1.2	0.0	0.4	0.3	0.0	0.7	1.4

* oral penicillin breakpoint, **NM = non-meningeal breakpoint

Conclusions:
If infant or adult PCV13 vaccination programs reduce the proportion of PCV13 STs in adult IPD, resistance to beta-lactam antibiotics can be expected to decrease, but erythromycin resistance will not change substantially, and resistance to fluoroquinolone antibiotics can be expected to increase.

Methods

- Since 1993, CBSN has collected all SPN sterile site isolates, and a sample of non-sterile pneumococcal isolates from participating Canadian hospitals and private microbiology labs (Figure 1). In total, 186 labs have participated with 40 labs submitting for the entire surveillance period.
- A single isolate per patient episode is included.
- Isolates are shipped to the central lab at Mount Sinai Hospital where they are confirmed as SPN, and broth microdilution susceptibility testing is performed and interpreted using CLSI standards.
- Since 2000, all sterile site isolates have been serotyped. Serotyping is performed using latex agglutination (Statens Serum Institute, DK) and Quellung reaction as required.

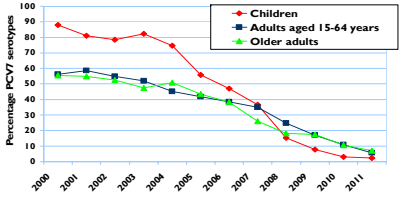
Figure 1. Canadian regions represented in the Canadian Bacterial Surveillance Network

Results

From 2000 to 2011, 10,305 SPN isolates were submitted that were obtained from sterile sites. These included: 9,527 (92.5%) from blood cultures, 297 (2.9%) from CSF, 208 (2.0%) from pleural fluid, and 273 (2.7%) from other sterile sites. There were 2,177 (21.2%) paediatric isolates, 4,482 (43.7%) isolates from adults aged 15-64 years, and 3,595 (35.1%) isolates from older adults (>=65 years). Overall, 61% of isolates were from Ontario, 18% from the Prairies/Northwest Territories, 8.8% from Atlantic provinces, 6.7% from Quebec, and 5.5% from British Columbia/Yukon.

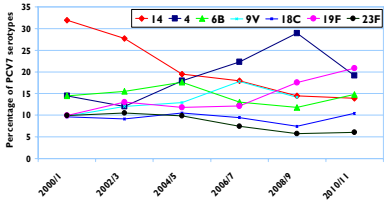
PCV7 was authorized for use in Canada in June 2001, and introduced into publicly funded infant immunization programs in provinces and territories between September 2001 and January 2005. Coincident with the introduction of these vaccination programs, the proportion of strains due to serotypes included in PCV7 declined in all age groups (see Figure 1).

Figure 1. Percentage of pneumococcal isolates from sterile sites belonging to serotypes covered by PCV7, CBSN surveillance, 2000 to 2011



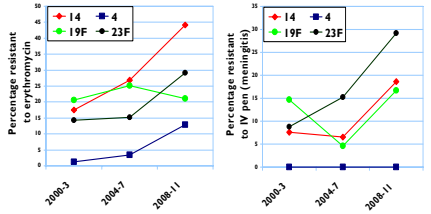
While the frequency of all serotypes included in PCV7 decreased over time, the changes were not uniform across serotypes. As shown in Figure 2, serotype 14, which was the most common serotype prior to PCV7 introduction, decreased most rapidly, comprising 32% of all PCV7 isolates in 2000/2001, but only 14% in 2010/11. In contrast, serotype 19F, which comprised 10% of PCV7 isolates in 2000/2001, comprised 21% in 2010/11.

Figure 2. Distribution of serotypes within the PCV7 group over time, CBSN surveillance, 2000 to 2011



Antibiotic resistance rates are increasing over time, but are different in different serotypes, and resistance rates change differently over time. Thus, changes in resistance depend on the interaction between selective pressure for resistance, and changing serotype distribution.

Figure 3. Percentage of pneumococcal isolates from sterile sites belonging to serotypes covered by PCV7, CBSN surveillance, 2000 to 2011



Results (cont'd)

By 2011, isolates with serotypes included in PCV7 contributed only 6.3% of isolates. Although resistance continues to increase in these serotypes, they are uncommon and their incidence continues to decrease. Thus, antimicrobial resistance in *S. pneumoniae* overall will be driven by the evolution of resistance in other serotypes. In 2011, isolates from serotypes included in PCV13 comprised 43.4% of all strains from adult sterile sites in CBSN surveillance: serotypes 19A and 7F were the most common conjugate vaccine strains (Figure 4a). Non-conjugate vaccine serotypes comprised 50.3% of all strains; the most common non-conjugate vaccine serotypes were 22F and 6C (Figure 4b).

Figure 4a: Frequency of occurrence of serotypes in conjugate vaccines in pneumococci from sterile sites in adult patients, CBSN surveillance, 2011

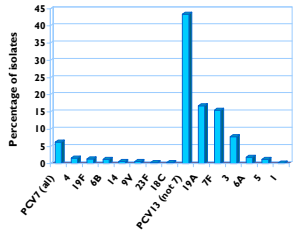
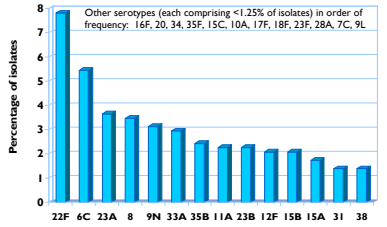
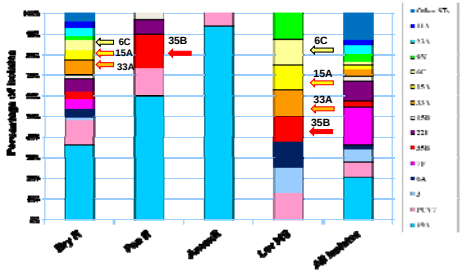


Figure 4b: Frequency of occurrence of serotypes not included in conjugate vaccines in pneumococci from sterile sites in adult patients, CBSN surveillance, 2011



As shown in Figure 5, all amoxicillin resistant isolates are of serotypes 19A and 19F. Serotype 19A and PCV7 serotypes are over-represented in erythromycin resistant isolates and penicillin resistant isolates, but not isolates with reduced susceptibility to respiratory fluoroquinolones. Serotypes 33A, 35B, 15A, 15C and 6C are over-represented in resistant isolates.

Figure 5: Distribution of serotypes in all adult sterile site isolates, compared to resistant adult sterile site isolates, CBSN surveillance, 2011



Results (cont'd)

If routine infant PCV13 vaccination programs are as effective as PCV7 against the 6 serotypes in PCV13 that are not contained in PCV7, and if, as expected, PCV7 serotypes continue to decline in frequency, PCV13 serotypes would be expected to comprise no more than 10% of all isolates by the year 2015.

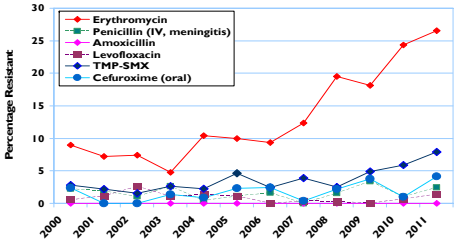
In this case, if amoxicillin resistance does not emerge in new serotypes, amoxicillin resistance should remain stable at 2% or less (resistance in serotype 19A may climb from the current 11%, but the proportion of disease due to serotype 19A should decline to less than 10% of all isolates). Resistance would be expected to decrease for antibiotics other than amoxicillin.

As shown in Figure 6, resistance to erythromycin can be expected to continue to increase steadily.

Resistance to respiratory fluoroquinolones has remained low, and is distributed among multiple serotypes, most likely because resistance arises due to mutations under antibiotic pressure in many individual isolates.

Trends in resistance to penicillin, cephalosporins and TMP-SMX are more difficult to predict. Although resistance has not increased significantly in penicillin and ceftriaxone, the significant increases in resistance to oral cefuroxime and TMP-SMX are of concern.

Figure 6. Antibiotic resistance in adult sterile site isolates of pneumococci of serotypes not included in any conjugate vaccine, CBSN, surveillance 2000-2011



Conclusions

- Erythromycin resistance has been increasing steadily. Although PCV13 serotypes are more likely to be erythromycin resistant than other serotypes, the overall, continuing increase means that the introduction of PCV13 will have little apparent impact.
- Resistance to respiratory fluoroquinolones remains low. PCV13 programs are expected to have minimal impact on resistance rates.
- The impact of PCV13 programs on amoxicillin resistance in adult sterile site isolates depends essentially entirely on whether these programs will provide effect herd immunity against infections due to serotype 19A.

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