Surveillance for antimicrobial resistance in *Streptococcus pneumoniae* in Canada, 1993–2011

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CBSN Canadian Bacterial Surveillance Network

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Abstract (Updated)

Background: Antibiotic use, vaccination programs, and changing patterns of underlying illness all contribute to changes in antimicrobial resistance in pneumococci. Monitoring trends is essential to guide empiric therapy for suspected pneumococcal infection.

Methods: CBSN is a collaborative network of hospitals/microbiology laboratories from all provinces/2 territories in Canada that has monitored resistance trends in SPN since 1993. Participating sites submit bacterial isolates to a central laboratory for antimicrobial susceptibility testing, performed to CLSI standards.

Results: From 1993 to 2011, 37,041 SPN isolates have been submitted: 39% from sterile sites (blood/CSF/pleural fluid/other), 37% respiratory sites (sputum/BAL), 22% other sites; 73% of isolates are from adults. From 1993/4 to 2011, R increased significantly (p<.001) to all ABs except FQ: pen [7.9% (241/3052) in '93/4 to 18.5% (304/1640) in 2011], amox [0% to 4.5%], ctx [0.0% – 0.5%], ery [3.3% – 29%], tet [2.2% – 15%], ts [4.6% – 12%], levo [0.8% – 1.1%]. Trends in antimicrobial resistance are shown in Table 1.

Table 1. Trends in antimicrobial resistance in pneumococcal disease, Canada, 1993 to 2011

	Year																		
% Resistant	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Pen R*	5.7	8.1	8.8	11.9	13.6	15.0	13.4	12.4	14.4	15.2	14.9	14.8	15.2	15.3	17.0	16.8	20.5	19.2	18.5
Amox R**	0.0	0.0	0.0	0.0	0.1	0.1	0.2	0.0	0.4	0.6	1.1	1.1	1.1	1.4	1.6	2.2	3.2	3.8	4.5
Eryth R	1.9	3.4	3.2	4.8	6.8	10.5	9.8	11.2	12.8	14.2	15.9	17.9	19.1	19.3	22.2	21.5	24.3	26.6	28.5
Clinda R	0.0	1.7	1.3	2.4	3.6	5.1	4.4	5.5	5.8	6.4	7.3	8.1	8.2	8.6	9.6	8.6	10.7	11.7	13.1
T/S R	3.8	4.6	9.7	12.7	14.6	12.3	12.0	11.3	12.0	13.2	13.3	13.5	12.1	11.9	11.9	11.4	13.5	14.0	12.1
Tet R	1.4	2.3	3.4	2.5	6.4	9.1	7.1	5.5	9.1	9.6	9.7	10.8	10.3	10.9	12.8	9.6	12.6	13.2	14.9
Ceftrx R*	0.0	0.2	0.1	0.7	1.3	2.5	1.5	2.0	2.4	1.5	1.8	2.5	1.9	3.7	3.0	3.3	4.8	4.3	5.3
Ceftrx R**	0.0	0.0	0.0	0.2	0.1	0.1	0.3	0.1	0.1	0.2	0.2	0.1	0.2	0.2	0.3	0.2	0.6	0.4	0.5
Levo R	0.0	1.5	0.1	0.2	0.5	0.3	0.4	0.9	1.2	1.9	1.2	1.5	1.5	1.7	1.1	1.5	1.3	0.7	1.1
Moxi R	NT	NT	0.0	0.0	0.3	0.2	0.2	0.4	0.4	0.3	0.4	0.6	0.7	0.9	0.6	0.7	0.5	0.4	0.4

*meningococcal breakpoints **non-meningococcal breakpoints

In 2010/11, 16% of isolates were 19A, 9% serotype 3, and 8% 7F. 98% of amoxicillin R isolates were ST 19A/19F.

Conclusions:
In 2011, R increased in all AB, except penicillin and TMP-SMX. Ery R rates now preclude the use of macrolides as empiric therapy. The significant increase in resistance to amoxicillin is also of concern.

Methods

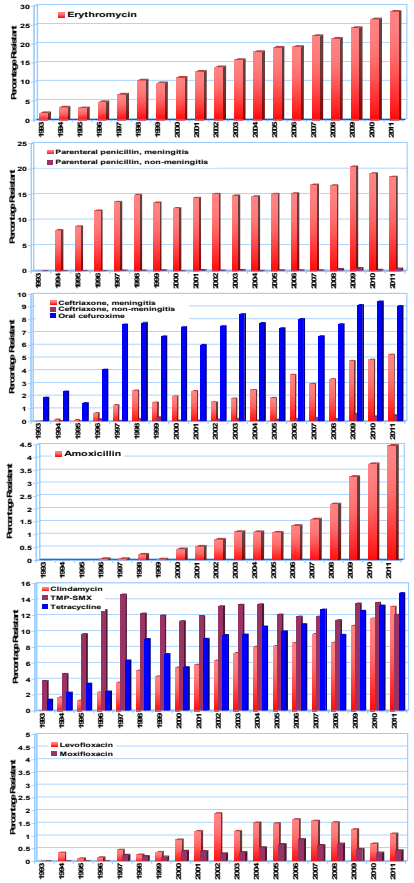
Figure 1. Canadian regions represented in the Canadian Bacterial Surveillance Network

- 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 frozen.
- Broth microdilution susceptibility testing is performed and interpreted using CLSI standards.
- Serotyping is performed using latex agglutination (Statens Serum Institute, DK) and Quellung reaction as required.

Results

From 1993 to 2011, 37,041 SPN isolates were submitted, including 14,544 (39.4%) from sterile sites (13,489 blood, 446 CSF, 285 pleural fluid, 324 from other sterile sites) and 22,380 from non-sterile sites (12,262 sputum/ETT, 1,491 bronchoscopy specimens, 5,150 eye swabs, 2,237 ear swabs, 1,240 other specimens). Paediatric cases (<15yrs) represented 26.9% of cases (N=9,661), younger adults (15-64 years) 39.5% of cases, and older adults (>=65yrs) 33.6% of cases. Overall, 56% of isolates were from Ontario, 17% from the Prairies/Northwest Territories, 12% from Atlantic provinces, 8% from Quebec, and 6% from British Columbia/Yukon.

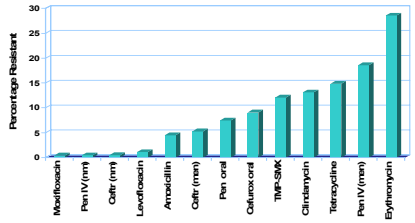
Figure 2. Percent of pneumococcal isolates resistant to various antibiotics, CBSN surveillance, 1993 to 2011



Results (cont'd)

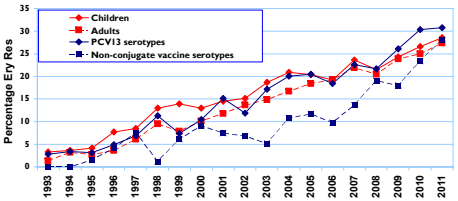
Antibiotic resistance has increased for all classes of antibiotics, although in 2011 pneumococci remain highly susceptible to moxifloxacin (prevalence of resistance 0.42%), parenteral penicillin for non-meningeal infections (prevalence of resistance 0.49%) and ceftriaxone for non-meningeal infections (prevalence of resistance 0.43%).

Figure 3. Antibiotic resistance in pneumococci in Canada, CBSN surveillance, 2011



The patterns of resistance differ for different antibiotics. Resistance to erythromycin, clindamycin and tetracycline has increased steadily year over year. Overall, erythromycin resistance is about 3% greater in isolates from respiratory sites than isolates from other sites, about 3% greater in isolates from children than from adults, and about 8% higher in isolates of serotypes included in PCV13 as compared to non-conjugate vaccine serotypes. However, as shown in Figure 4, for different age groups and PCV13 vs. non-conjugate vaccine serotypes, erythromycin resistance is increasing steadily in all population subgroups.

Figure 4. Percent of isolates resistant to erythromycin in different subgroups, CBSN surveillance, 1993 to 2011



Resistance to respiratory fluoroquinolones rose to a peak in 2002 and has since remained stable or slightly decreased. This temporal pattern is present in all age groups, in isolates from different body sites, and in isolates of different serotypes (data not shown). Factors associated with resistance to respiratory fluoroquinolones are shown in Table 2 below.

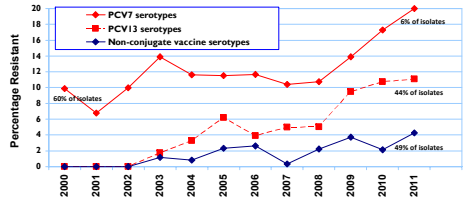
Table 2. Levofloxacin resistance in Canada by age, site, and serotype groups, 1993 to 2011

	Levofloxacin resistance overall, 1993-2011	Levofloxacin resistance, 2011	P-value
Age group			
Children (<15 years)	0.06%	0.00%	<.001
Adults 15-64 years	0.73%	0.49%	
Adults ≥65 years	2.25%	2.44%	
Isolate type			
Respiratory	2.06%	1.91%	<.001
Sterile site	0.40%	0.45%	
Serotype category			
Included in PCV13	0.79%	0.69%	<.001*
Not included in PCV13	2.06%	1.79%	

Results (cont'd)

Resistance to penicillin and the cephalosporins increased in the mid- to late-1990s, primarily due to increasing resistance in serotypes contained in the PCV7 conjugate vaccine. The introduction of PCV7 routine infant vaccination programs beginning in 2001, and the consequent decrease in disease due to serotypes contained in PCV7, resulted in an overall stabilization of penicillin and cephalosporin resistance until about 2008, when emerging resistance in serotypes included in PCV13 but not PCV7 began to increase (Figure 5 below). To date, resistance to cephalosporins has remained low in serotypes not included in any conjugate vaccines; however, the suggestion of increasing resistance in this serotype category is of some concern.

Figure 5. Percent of sterile site isolates resistant to oral cefuroxime, by year and by serotype category, CBSN surveillance, 2000 to 2011



Amoxicillin resistance has occurred in a very limited number of serotypes, which are all, except 35B, included in the PCV13 vaccine. Of 422 amoxicillin resistant isolates identified in surveillance, 201 (48%) are serotype 19A, 183 (43%) are serotype 19F, 27 (6.4%) are serotype 14, 9 (1.5%) are serotype 23F, 1 (0.2%) is serotype 6A and 1 (0.2%) is serotype 35B.

In isolates from invasive pneumococcal disease, amoxicillin resistance was first identified in serotype 19F in 1999, increased to 11% in 2003 and has since remained relatively stable. In serotype 19A, amoxicillin resistance was first detected in 2005 in 3 of 43 sterile site isolates (7%). Since then, amoxicillin resistance in serotype 19A has increased steadily to 14% in 2011.

Conclusions

- Erythromycin resistance has been increasing steadily in all types of isolates and infections in all age groups. The introduction of vaccines has had very little apparent impact, and the introduction of PCV13 will likely not result in any reduction in erythromycin resistance. Rates of resistance are such that macrolides should not be used when pneumococcal infection is strongly suspected.
- Resistance to respiratory fluoroquinolones remains low and is of potential significance only in respiratory isolates from older adults. Conjugate vaccine serotypes are less likely to be resistant to fluoroquinolones than other serotypes.
- Amoxicillin resistance has been identified only in serotypes included in conjugate pneumococcal vaccines. In 2010–2011, 19A comprised 16% of all isolates and is over-represented among resistant isolates (33% of erythromycin R, 75% of penicillin R (non-meningeal), and 75% of amoxicillin R).

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