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Trends In Antimicrobial Resistance in *Streptococcus pneumoniae*, Canada, 1993-2009

K. A. GREEN*, A. MCGEER, A. PLEVNESHI, S. PONG-PORTER, K. HASSAN, W. RUDNICK, D. E. LOW, Canadian Bacterial Surveillance Network (CBSN);
Mount Sinai Hospital, Toronto, Ontario, Canada.

Contact: Karen Green
Tel: (416) 586-5105
Fax: (416) 586-3140
kgreen@mtsinai.on.ca

CBSN Canadian Bacterial Surveillance Network

Abstract (updated)

Background: The Canadian Bacterial Surveillance Network (CBSN) has been monitoring resistance trends in Canadian isolates of S. pneumoniae (SP) since 1993.
Methods: CBSN is a collaborative network of microbiology laboratories from across Canada that submit bacterial isolates to a central laboratory for broth microdilution antimicrobial susceptibility testing performed according to CLSI standards.
Results: Of the 33,361 SPN isolates submitted and tested between 1993 and December of 2009, 37 % were from blood/CSF (blood: 35%; CSF: 1%), 37% from sputum/resp. specimens, 26% from other sites. The trends in antimicrobial susceptibility are expressed below as percentage resistant.

Year	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Pen NS	5.7	8.1	8.8	11.9	13.6	15.0	13.4	12.3	14.4	15.2	14.9	14.8	15.3	15.3	17.2	16.8	20.3
Pen R	0.9	1.3	2.2	4.1	6.6	5.7	5.9	5.9	6.8	6.6	6.2	5.4	4.8	6.3	4.6	6.6	8.3
Amox R	0.0	0.0	0.0	0.0	0.1	0.1	0.2	0.1	0.5	0.6	1.1	1.1	1.1	1.4	1.6	2.2	3.4
Eryth R	1.9	3.4	3.2	4.8	6.8	10.5	9.8	11.2	12.8	14.2	15.9	18.0	19.1	19.4	22.5	21.6	24.3
Clinda R	0.0	1.7	1.3	2.4	3.6	5.1	4.4	5.5	5.8	6.5	7.4	8.1	8.2	8.6	9.7	8.7	11.0
T/S R	3.8	4.7	9.7	12.7	14.6	12.3	12.0	11.3	12.0	13.2	13.3	13.5	12.2	11.8	12.0	11.4	13.8
Tet R	1.4	2.3	3.4	2.5	6.4	9.1	7.1	5.5	9.1	9.6	9.7	10.9	10.4	11.2	13.1	9.9	12.6
Ceftrx R (M)*	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	2.9	3.3	5.1
Ceftrx R (NM)**	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	0.7
Cipro R ¶	0.5	0.8	0.7	0.8	1.8	1.8	1.6	1.4	2.1	2.7	1.8	2.0	2.4	2.7	2.0	2.2	1.5
Levo R	0.0	0.4	0.1	0.2	0.5	0.3	0.4	0.9	1.2	1.9	1.2	1.5	1.5	1.7	1.2	1.5	1.3
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	0.7	0.7	0.4

*M= meningeal breakpoint, **NM = non-meningeal breakpoint, ¶ breakpoint used for reduced susceptibility ≥4μg/mL, NT = not tested

Preliminary results from 2009 suggest increasing resistance in all classes of antibiotics except fluoroquinolones. From 2008 to 2009, erythromycin resistance and tetracycline resistance increased from 21.6% to. 24.3% (p=0.06) and from 9.9% to. 12.6% (p=0.01), respectively. Resistance to clindamycin increased from 8.7% in 2008 to 11.0% in 2009 (p=0.02). Penicillin resistance increased from 6.6% in 2008 to 8.3% in 2009 (p=0.09). Ceftriaxone resistance (meningeal breakpoint MIC >=2) increased from 3.3% in 2008 to 5.1% in 2009 (p=0.009). Amoxicillin resistance continued to increase: to 3.4% in 2009 from 2.2% in 2008 and 1.6% in 2007 (p=0.03). In contrast, resistance to ciprofloxacin, levofloxacin, and moxifloxacin decreased slightly between 2008 and 2009 (cip 2.2% vs 1.5%, p=0.14; levo 1.5 vs. 1.3%, p=0.52; moxi 0.7 vs. 0.4, p=0.18).
Conclusions: In 2009, antimicrobial resistance increased to penicillin, amoxicillin, ceftriaxone, erythromycin, trimethoprim/sulfa and tetracycline. Resistance to ciprofloxacin, levofloxacin and moxifloxacin decreased slightly. Moxifloxacin remains the most active agent against pneumococci in Canada.

Background

The Canadian Bacterial Surveillance Network (CBSN) is a network of microbiology laboratories from across Canada that submit bacterial isolates to a central laboratory for standardized antimicrobial susceptibility testing. This group has been monitoring resistance trends in Canadian isolates of *Streptococcus pneumoniae* and examining potential molecular and epidemiological drivers of resistance since 1988.

* Other members of the Canadian Bacterial Surveillance Network and their participating laboratories are as follows: Karl Weiss, Hopital Maisonneuve-Rosemont, University of Montreal, Montreal, Quebec; George Zhanel and Daryl Hoban, Health Sciences Center, Winnipeg, Manitoba; Magdalena Kuhn, Southeast Healthcare Corp.-Moncton Site, Moncton, New Brunswick; Deirdre Church, Calgary Laboratory Services, Calgary, Alberta; Ross Davidson and Kevin Forward, QEII Elizabeth Health Sciences Center, Halifax, Nova Scotia; Andrew Simor, Sunnybrook Health Sciences Center, Toronto, Ontario; H. R. Devlin, St. Michael's Hospital, Toronto, Ontario; R. G. Lewis, Cape Breton Regional Health Care Complex, Sydney, Nova Scotia; P. C. Kibsey, Victoria General Hospital, Victoria, British Columbia; J. Blondeau, Royal University Hospital, Saskatoon, Saskatchewan; G. K. Harding, St. Boniface General Hospital, Winnipeg, Manitoba; L. Thibault, Dr. Georges L. Dumont Hopital, Moncton, New Brunswick; F. Smaill, Hamilton Health Sciences Corp., Chedoke-McMaster, Hamilton, Ontario; M. Gourdeau and G. Murray, Hopital de l'Enfant-Jesus, Laval University, Quebec City, Quebec; S. Richardson and A. Matlow, Hospital for Sick Children, Toronto, Ontario; G. J. Hardy, Saint John Regional Hospital, Saint John, New Brunswick; P.R. Laberge, Centre Hospitalier Regional de Sept-Iles, Sept-Iles, Quebec; L. P. Abbott, Queen Elizabeth Hospital, Charlottetown, Prince Edward Island; M. Yorke, Westman Regional Laboratory, Brandon, Manitoba; N. Clerk and Z. Mooloo, William Osler Health Center, Etobicoke, Ontario; J. Downey and P. Da Camara, Toronto East General and Orthopedic Hospital, Inc., Toronto, Ontario; M. Bergeron, CHUQ-Ctr Hopital, Université Laval, Sainte-Foy, Québec; J. Hutchinson, Health Care Corp., St. John's, Newfoundland; S. Krajden, St. Joseph's Health Care Center, Toronto, Ontario; R. Price, Royal Victoria Hospital, Barrie, Ontario; J. F. Paradis, Hopital de Chicoutimi, Chicoutimi, Quebec; L. Bocci, Regional Hospital Centre, Bathurst, New Brunswick; M. Savard and David Thompson Regional Laboratories, Red Deer, Alberta; K. Ostrowska, Trillium Health Centre, Mississauga, Ontario; P. Pieroni, Provincial Laboratory, Regina, Saskatchewan; B. Mederski and K. Katz, North York General Hospital, Toronto, Ontario; C. Tremblay, Hotel Dieu de Quebec, Quebec City, Quebec; P. Leighton, Dr. Everett Chalmers Hospital, Fredericton, Nova Scotia; D. Yamamura,, MDS Laboratories, Toronto; D. Noria and A. Gelbloom, The Scarborough Hospital, Toronto; A. Sarabia, Credit Valley Hospital, Toronto, Ontario; D. Chen, York County Hospital, Toronto, Ontario and Southlake Health Centre, Newmarket, Ontario; and N. Rau, Halton Health Services, Oakville, Ontario.

Methods

CBSN is a collaborative group of hospitals and private microbiology laboratories from all 13 provinces and territories of Canada. Each year, laboratories, based on their size, are asked to submit the first 20 or 100 consecutive isolates of *S. pneumoniae* from all sites, as well as all sterile site isolates for the year. Only one isolate per patient is included. A total of 186 laboratories have participated since 1993, including 19 private laboratories, and 164 laboratories serving hospitals ranging in size from 18 to 1325 beds. Participation is voluntary, and varies from year to year; however, a representative core group of ~50 laboratories have submitted for the entire surveillance period. Isolates are shipped to the central study laboratory at the Mount Sinai Hospital, where they are confirmed as *S. pneumoniae* and frozen. Broth microdilution susceptibility testing is performed and interpreted using CLSI standards.

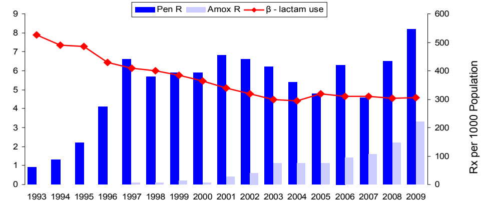
Results

Between 1993 and 2008, 33,369 isolates of *S. pneumoniae* were collected and tested. Characteristics of pneumococcal isolates by year are shown in Table 1 below.

Year	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
No. of isolates	212	2840	1739	1180	1510	1428	2106	2193	2242	2519	2423	2552	2664	2224	2062	2010	1516
No. labs submitting	28	119	102	79	76	68	74	64	62	70	70	65	63	59	57	54	42
Source of Isolate (%)																	
Respiratory	39.2	39.2	32.0	23.8	40.7	38.6	32.4	25.0	28.0	39.8	42.8	44.0	45.4	47.0	45.4	41.37	42.0
Sterile sites	34.4	22.4	44.7	63.7	38.5	39.4	40.7	40.7	42.9	37.9	37.2	37.2	32.6	31.5	36.6	40.33	44.9
Other	36.4	38.5	23.4	12.5	21.9	21.9	26.8	31.7	29.1	22.3	20.0	18.8	22.0	21.5	18.0	17.50	13.3
Age in years (%)																	
≥ 65	32.9	26.9	34.3	35.8	36.6	37.2	33.9	31.6	29.4	33.2	33.6	33.6	33.9	36.2	35.3	35.8	35.9
16-64	29.8	30.6	33.7	33.3	33.3	32.6	33.9	32.3	33.9	38.8	38.8	41.5	42.9	44.9	46.7	49.7	47.6
≤ 15	37.3	42.5	32.0	30.9	30.1	30.3	32.2	36.1	36.7	28.0	27.6	24.6	24.3	18.9	18.0	14.4	16.5
Geographic Area (%)																	
Western Canada	39.2	30.0	22.4	35.2	26.0	26.9	20.5	20.9	24.5	21.5	23.1	22.4	17.9	27.5	20.7	23.48	24.0
Ontario	24.5	55.5	63.7	52.4	47.6	53.7	54.5	52.9	48.4	56.9	56.3	55.7	55.5	50.6	54.0	56.35	69.0
Quebec	11.4	4.7	4.9	7.8	7.4	10.2	12.7	12.7	13.8	10.3	8.6	7.9	11.5	9.2	12.1	5.75	0.10
Atlantic Canada	25.0	9.8	9.0	4.6	19.0	9.2	12.3	13.5	13.3	11.3	12.0	14.0	14.26	12.7	13.2	14.42	6.9

Penicillin resistance (MIC ≥ 2μg/ml) increased significantly from 0.9% in 1993 to 6.6% in 1997 (P<0.0001), remaining stable until 2009 when it increased slightly to 8.3% (p=0.09). Amoxicillin resistance has increased steadily from 0.24% in 1999 to 3.4% in 2009 (P<.00001). β-lactam use decreased significantly from 525 Rx/1000pop in 1993 to 320 Rx/1000 pop in 2005 and has remained stable since. (Figure 1)

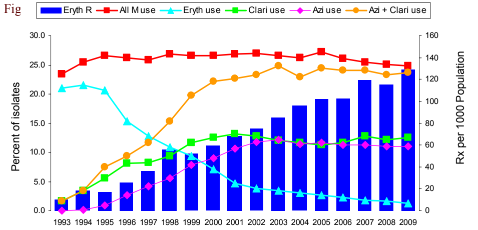
Figure 1. β-lactam use and pneumococcal resistance rates



Results (con't)

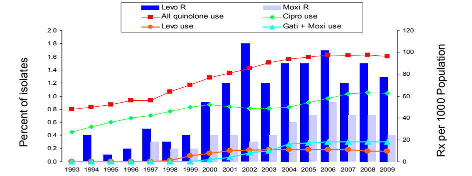
Erythromycin resistance increased significantly from 1.9% in 1993 to 22.4% in 2007 (P<0.0001) (Figure 2). In 2008, erythromycin resistance decreased slightly to 21.1% (P=0.439) with a subsequent increase to 24.3% (p=0.06) in 2009.Between 1993 and 2005, total macrolide use increased from 125 to 145 Rx/1000 pop and has decreased annually in subsequent years to 132 Rx/1000 pop in 2009. However, the types of macrolides used changed over this time period. Erythromycin use decreased from 115 Rxs/1000 pop in 1994 to 7 Rx/1000 pop in 2009. Azithromycin and clarithromycin became the macrolides of choice with a sustained increase from 9 to 67 Rx/1000 pop for clarithromycin between 1994 and 2000 and a parallel increase in Rx rates for azithromycin from 1 Rx/1000 pop in 1994 to 63 Rx/1000 pop in 2002. Since 2003 use of all three macrolides has decreased or remained relatively unchanged (Figure 2).

Fig



Levofloxacin resistance increased from 1993 to 2002 then remained stable until 2007 when it decreased from 1.8% in 2006 to 1.2% (P=0.05).Levo resistance increased slightly to 1.5% in 2008 and decreased again to 1.3% in 2009. Moxifloxacin resistance has decreased from its highest rate of 0.9% in 2006 to 0.4% in 2009 (P=0.09). Total fluoroquinolone use increased steadily from 48 Rx/1000 pop in 1993 to 97 Rx/1000 pop in 2007. Ciprofloxacin use increased from 27 Rx/1000 pop to 62 Rx/1000 pop over the same time period. Respiratory fluoroquinolone use also increased: levofloxacin from 1 Rx/1000 pop in 1998 to 11 Rx/1000 pop in 2005, gatifloxacin from 0 in 1999 to 3.7 Rx/1000pop in 2002 to 8 Rx/1000 pop in 2005 when active marketing of the product was discontinued in Canada. The use of moxifloxacin increased from 3.5 Rx/1000 pop in 2000 to 18 Rx/1000 pop in 2006 and has remained stable (Figure 3).

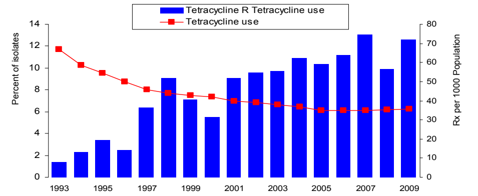
Figure 3. Fluoroquinolone use and pneumococcal resistance rates



Results (con't)

Tetracycline non-susceptibility increased steadily from 1.9% in 1993 to 13.4% in 2007 (P<0.0001). A slight decrease in tetracycline resistance was evident in 2008 (9.8%, P=0.006) but has increased again in 2009 to 12.6%(p=0.01). From 1993 to 2005, use of tetracycline decreased from 67 Rx/1000 pop to 35 Rx /1000 pop and has remained stable.

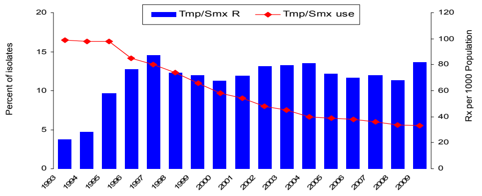
Figure 4. Tetracycline use and pneumococcal resistance rates



Among tetracycline non-susceptible isolates erythromycin non-susceptibility has increased from 50.8% in 1994 to 91.8% in 2009 (χ2, p<0.0001).

TMP/SMX non-susceptibility increased significantly from 9.4% in 1993 to 22.5% in 1997 (P<0.0001), with no significant change in rates until 2009 (13.8, p=0.04). TMP/SMX use has steadily decreased from 99 Rx/1000 pop in 1993 to 33 Rx/1000 pop in 2009.

Figure 5. TMP/SMX use and pneumococcal resistance rates



Conclusions

In Canada, pneumococcal resistance to beta-lactam antibiotics, macrolides, tetracycline and trimethoprim sulfa continues to increase. Resistance to fluoroquinolones remains low. The increasing trend in resistance to amoxicillin is of concern (χ2, p<0.0001).