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Current Epidemiology and Antimicrobial Resistance of *Streptococcus pneumoniae* (SPN) in Canada: SAVE 2014

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ABSTRACT

Background: The SAVE study (SPN Serotyping and Antimicrobial Susceptibility: Assessment for Vaccine Efficacy in Canada) is an annual, ongoing study that was initiated in 2011, after PCV-13 was introduced in Canada.
Methods: In collaboration between CARA and the National Microbiology Laboratory, the SAVE study collected 5012 invasive isolates in 2011-14 from across Canada (1379, 1285, 1138 and 1210 in 2011, 2012, 2013 and 2014 respectively). Serotyping was performed using the Quellung reaction (Statens Serum Institute, Copenhagen, Denmark). Susceptibility testing (AST) was performed in accordance with CLSI methods. Changes in serotype (ST) distribution and multi-drug resistance (MDR) rates between 2011 and 2014 were assessed for statistical significance.
Results: In 2014, 25.4% of the currently circulating SPN STs are contained in PCV-13; however, significant differences are noted by region (West: 16.4% - East: 31.7%) and age group (0-<1 year: 0% - 6-<18 years: 33.3%). The susceptibility results of the 10 most common STs in 2014 are shown below.

Serotype (N)	% Susceptible								% MDR
	PEN (iv, M)	PEN (iv, NM)	CRO (M)	CRO (NM)	CLR	LVX	SXT	DOX	
22F (116)	100	100	100	100	70.4	97.4	97.4	100	0.9
3 (96)	100	100	100	100	95.6	100	100	86.7	3.3
19A (86)	76.7	89.5	86.1	98.8	36	100	74.4	74.4	16.3
11A (82)	97.6	100	97.6	100	72	100	81.7	97.6	3.7
7F (71)	100	100	100	100	95.7	100	98.6	95.7	0
16F (61)	100	100	100	100	100	93.3	97.8	100	0
12F (52)	100	100	100	100	55.8	100	100	100	0
9N (51)	98	100	100	100	88.2	100	98	100	0
8 (48)	100	100	100	100	100	100	100	93.6	0
33F (44)	100	100	100	100	22.7	100	29.5	84.1	6.8

M, meningitis; NM, nonmeningitis; PEN, penicillin; CRO, ceftriaxone; CLR, clarithromycin; LVX, levofloxacin; SXT, trimethoprim-sulfamethoxazole; DOX, doxycycline; MDR, multi-drug resistance [resistance to ≥ 3 antibiotic classes (penicillin resistance defined as MIC ≥ 2 µg/ml)]
Significant changes (P<0.05) in ST prevalence between 2011 and 2014 were noted as decreased prevalence of STs 4, 5, 7F, 19A and 33A and increased prevalence of STs 10A, 11A, 13, 16F, 20, 24F, 29, 31, 33F, 35B, 35F and 9N. Current MDR was noted in STs 3 (3.3%), 6B (100%), 9V (33.3%), 11A (3.7%), 15A (50%), 19A/F (16.3/37.5%), 22F (0.9%), 23A (2.6%), 24F (20%), 29 (10%) and 33F (6.8%). MDR SPN rates decreased from 8.6% in 2011 to 4.1% in 2014 (P<0.0001).
Conclusion: In 2014, 25.4% of all circulating SPN and 52.1% of MDR SPN in Canada are ST included in PCV-13. Significant changes in the epidemiology and AST patterns continue to occur in SPN in Canada, warranting ongoing study.

BACKGROUND

The introduction of Prevnar® (PCV-7), a 7-valent pneumococcal conjugate vaccine, was effective in reducing systemic infections due to *Streptococcus pneumoniae* in children as well as reducing the incidence of recurrent upper respiratory tract infections in children.[1,2] However, the emergence of non-PCV-7 *S. pneumoniae* serotypes in Canada, particularly multi-drug resistant strains was of significant concern. Subsequently, newer pneumococcal conjugate vaccines were developed with enhanced serotype coverage, including Prevnar®13 (PCV-13). The broader serotype coverage and critical inclusion of serotype 19A in PCV-13 offers an important advancement in the protection of Canadian children against invasive *S. pneumoniae* infections. Current immunization guidelines recommend the routine use of PCV-13 in North America.[3,4] The predominant serotypes and their antimicrobial susceptibility patterns are expected to continue to evolve over time.

The *S. pneumoniae* Serotyping and Antimicrobial Susceptibility: Assessment for Vaccine Efficacy in Canada (SAVE) study began in 2011 to assess the *S. pneumoniae* serotypes and their antimicrobial susceptibility patterns in Canada after the introduction of the PCV-13 vaccine. Changes in serotype (ST) distribution and multi-drug resistance (MDR) rates between 2011 and 2014 were assessed to evaluate the evolution of serotypes and antimicrobial resistance subsequent to the introduction of PCV-13 in Canada.

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MATERIALS & METHODS

Isolate Collection:

S. pneumoniae isolated from sterile sites are forwarded from Canadian public health laboratories [Canadian Public Health Laboratory Network (CPHLN)] to the National Microbiology Laboratory - Public Health Agency of Canada. Through a collaboration between the Canadian Antimicrobial Resistance Alliance (CARA) and the National Microbiology Laboratory – Public Health Agency of Canada and subsequent to the permission of the submitting CPHLN sites, the *S. pneumoniae* isolates were forwarded to CARA. A total of 5012 invasive *S. pneumoniae* isolates from across Canada were included in the SAVE study as part of this collaboration (Jan. 1, 2011 – Dec. 31, 2014) The annual number of *S. pneumoniae* collected were 1379, 1285, 1138 and 1210 in 2011, 2012, 2013 and 2014, respectively.

Antimicrobial Susceptibility Testing:

Antimicrobial susceptibility testing was performed using custom designed antimicrobial susceptibility panels using CLSI methods. These antimicrobials were obtained as laboratory grade powders from their respective manufacturers or commercial sources. The MICs of the antimicrobial agents for the isolates were determined by the broth microdilution method, which was performed in adherence to all CLSI practices and quality control measures, and interpreted utilizing CLSI criteria (M7-A9, M100-S23).

Multi-drug resistance was defined as resistance to ≥3 antimicrobial classes (penicillin MIC ≥ 2 µg/mL).

Serotyping:

Serotyping was performed using the Quellung reaction using pool, group, type and factor commercial antisera (Statens Serum Institute, Copenhagen, Denmark) and supplementary molecular serotyping was performed with the US Centre for Disease Control's PCR multiplex method (http://www.cdc.gov/ncidod/biotech/strep/pcr.htm). Isolates for which a serotype was not determined by PCR and a Quellung reaction was not observed were confirmed as *S. pneumoniae* by *rpo*B gene sequencing.

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CONCLUSIONS

1. In 2014, 25.4% of all circulating *S. pneumoniae* and 52.1% of MDR *S. pneumoniae* in Canada are serotypes in PCV-13.
2. The most commonly circulating serotypes are 22F, 3, 19A, 11A, 7F, 16F, 12F, 9N, 8, and 33F. Between 2011 and 2014, statistically significant reductions in the prevalence of vaccine serotypes 4, 5, 7F and 19A,were observed. Among non-vaccine serotypes, significant reductions in serotype 33A and increases in serotypes 10A, 11A, 13, 16F, 20, 24F, 29, 31, 33F, 35B, 35F and 9N occurred.
3. In 2014, multidrug resistance was observed in serotypes 3, 6B, 9V, 11A , 15A, 19A, 19F, 22F, 23A, 24F, 29 and 33F. Rates of multidrug resistance in *S. pneumoniae* significantly decreased from 8.6% in 2011 to 4.1% in 2014 (P<0.0001).
4. Significant changes in the epidemiology and antimicrobial susceptibility patterns continue to occur in *S. pneumoniae* in Canada, warranting ongoing study.

RESULTS

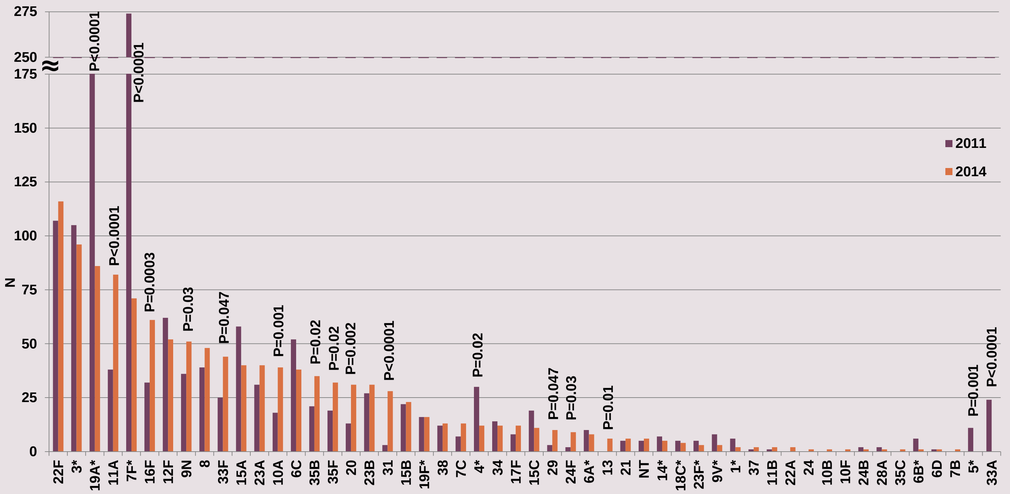

Figure 1. *S. pneumoniae* Serotype Distribution in Canada in 2014 compared to 2011
* PCV-13 Serotypes

Table 1. Proportion of Currently Circulating *S. pneumoniae* Serotypes Contained in PCV-13 by Age Group (2014)

	Age Group (years)							
	0 - <1 (N=25)	1 - <2 (N=45)	2 - <6 (N=42)	6 - <18 (N=24)	18 - <50 (N=226)	50 - <65 (N=346)	≥65 (N=483)	Not provided (N=19)
Non PCV-13 serotypes	25 (100%)	41 (91.1%)	33 (78.6%)	16 (66.7%)	170 (75.2%)	244 (70.5%)	362 (74.9%)	12 (63.2%)
PCV-13 serotypes	0 (0%)	4 (8.9%)	9 (21.4%)	8 (33.3%)	56 (24.8%)	102 (29.5%)	121 (25.1%)	7 (36.8%)

Table 2. Proportion of Currently Circulating *S. pneumoniae* Serotypes Contained in PCV-13 by Region (2014)

	Region			
	West (N=262)	Central (N=803)	East (N=46)	National
Non PCV-13 serotypes	219 (83.6%)	585 (72.9%)	99 (68.3%)	903 (74.6%)
PCV-13 serotypes	43 (16.4%)	218 (27.1%)	46 (31.7%)	307 (25.4%)

Antimicrobial Susceptibility Rates:

The antimicrobial susceptibility rates for all *S. pneumoniae* and PCV-13 serotypes in 2014 was as follows: penicillin (iv, nonmeningitis) 99.1% and 96.3%, penicillin (iv, meningitis) 91.0% and 88.9%, penicillin (oral) 91.0% and 88.9%, ceftriaxone (nonmeningitis) 99.8% and 99.3%, ceftriaxone (meningitis) 97.6% and 93.3%, clarithromycin 76.6% and 71.1%, levofloxacin 99.0% and 99.7%, trimethoprim-sulfamethoxazole 89.3% and 89.2%, and doxycycline 91.1% and 84.2%.

Multidrug Resistance:

Current MDR was noted in serotypes 3 (3.3%), 6B (100%), 9V (33.3%), 11A (3.7%), 15A (50%), 19A (16.3%), 19F (37.5%), 22F (0.9%), 23A (2.6%), 24F (20%), 29 (10%) and 33F (6.8%).

Of the 48 MDR *S. pneumoniae* in SAVE 2014, there were 21 isolates resistant to 3 classes of antibiotics, 12 resistant to 4 classes of antibiotics, 9 resistant to 5 classes of antibiotics, and 6 resistant to 6 classes of antibiotics. The most common MDR phenotypes demonstrated resistance to clarithromycin, clindamycin, and doxycycline (n=15), clarithromycin, clindamycin, doxycycline, penicillin, and trimethoprim-sulfamethoxazole (n=7) and chloramphenicol, clarithromycin, clindamycin, doxycycline, penicillin, and trimethoprim-sulfamethoxazole (n=6).

MDR *S. pneumoniae* rates decreased from 8.6% in 2011 to 4.1% in 2014 (P<0.0001).

Table 3. Demographics of the Common (n≥5) Multi-drug Resistant *S. pneumoniae* by Serotype in Canada (2014)

Serotype (N)	Geographic Region *	Age Group (years) 0-<1	1-<2	2-<6	6-<18	18-<50	50-<65	≥65	Region Total
19A (14)	West		2			1	3	1	7
	Central							2	3 [a]
	East						1	3	4
15A (13)	West					1	1	1	3
	Central					2	1	4	7
	East							3	3
19F (6)	West						2		2
	Central							3	3
	East						1		1

* West (Saskatchewan, Manitoba); Central (Ontario, Quebec); East (Prince Edward Island, Nova Scotia, New Brunswick, Newfoundland and Labrador); [a] No age data available for 1 additional serotype 19A isolate : from Central

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