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Antimicrobial Susceptibility Patterns of Common Invasive *Streptococcus pneumoniae* Serotypes in Canada: The SAVE Study

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Introduction

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 multidrug 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 Effectiveness 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 distribution and multidrug resistance (MDR) rates between 2011 and 2018 were assessed to evaluate the evolution of serotypes and antimicrobial resistance subsequent to the introduction of PCV-13 in Canada.

Materials and Methods

Isolate Collection

S. pneumoniae isolated from sterile sites are forwarded from the 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 select submitting CPHLN sites (as detailed in the acknowledgments), the *S. pneumoniae* isolates were forwarded to CARA. A total of 11,044 invasive *S. pneumoniae* isolates from across Canada were included in the SAVE study as part of this collaboration (Jan. 1, 2011 – Dec. 31, 2018) with 1878 collected in 2018.

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing was performed using custom designed in-house manufactured antimicrobial susceptibility panels using CLSI methods (5). MICs 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 (5,6). Multidrug 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.

Statistical Analysis

Trends in the proportion of MDR rates throughout the study were assessed for statistical significance using the Cochran-Armitage test.

Acknowledgements

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References

1) Bettinger, J.A. *et al*. 2010. Vaccine. 28:2130-2136. **2)** CDC. 2005. MMWR Morb. Mortal. Wkly. Rep. 54: 893-897. **3)** National Advisory Committee on Immunization. 2010. Can. Commun. Dis. Rep. 36: 1-21. **4)** CDC. 2010. MMWR Recomm. Rep. 59(RR-11): 1-18. **5)** CLSI. M07. Wayne, PA: CLSI; 2018. **6)** CLSI. M100. Wayne, PA: CLSI; 2019.

Results

Table 1. Antimicrobial susceptibilities of the ten most commonly collected serotypes, PCV-13 serotypes and all isolates of *S. pneumoniae* collected in SAVE 2018

Serotype (N)	% Susceptible								% MDR
	PEN (iv, M)	PEN (iv, NM)	CRO (M)	CRO (NM)	CLR	LVX	SXT	DOX	
3 (234)	100	100	100	100	92.3	100	99.2	86.3	6.0
22F (170)	99.4	100	99.4	100	52.9	100	99.4	98.2	2.4
8 (111)	100	100	100	100	97.3	100	100	98.2	0
9N (108)	95.3	100	100	100	87.9	100	98.1	98.1	0.9
19A (93)	71.7	83.7	80.4	94.6	19.6	98.9	73.9	72.8	25.0
12F (89)	100	100	100	100	40.5	100	96.6	96.6	2.2
11A (75)	89.3	98.7	97.3	97.3	61.3	100	81.3	92.0	8.0
15A (70)	44.2	100	88.4	100	41.9	100	97.7	44.2	55.8
23B (69)	53.6	100	100	100	92.8	100	78.3	97.1	2.9
33F (66)	100	100	100	100	10.6	100	13.6	95.5	3.0
PCV-13 (525)	89.5	95.8	98.3	98.3	77.3	99.1	85.5	85.7	10.3
All SPN (1878)	88.7	98.7	97.2	99.3	73.7	99.7	86.6	91.2	6.5

M, meningitis; NM, nonmeningitis; PEN, penicillin; CRO, ceftriaxone; CLR, clarithromycin; LVX, levofloxacin; SXT, trimethoprim-sulfamethoxazole; DOX, doxycycline; MDR, multidrug resistance.

Table 2. Annual Prevalence of MDR in *S. pneumoniae* in Canada, 2011-2018

Study Year	N [a]	MDR Rate (%)
2011	1362	8.5
2012	1230	6.8
2013	1099	5.9
2014	1219	3.9
2015	1215	5.7
2016	1227	3.9
2017	1544	6.7
2018	1833	6.5
P-value (2011-18) = 0.057		

[a] N for which complete susceptibility data available.

Table 3. Demographics of the Common (N≥5) MDR *S. pneumoniae* Serotypes in Canada (2018)

Serotype (N)	Geographic Region *	Age Group (years)							Region Total
		0-<1	1-<2	2-<6	6-<18	18-<50	50-<65	≥65	
15A (24)	West					2	1	1	4
	Central	1	1			2	4	10	18
	East						1	1	2
19A (23)	West	1				4	1	3	9
	Central			1	1	3	4	4	13
	East						1		1
3 (14)	West						1	2	3
	Central					6	3	2	11
	East								0
19F (8)	West								0
	Central					5	3		8
	East								0
23A (8)	West								0
	Central			2	1	2	2		7
	East						1		1
11A (6)	West								0
	Central					1	3	1	5
	East						1		1
35B (5)	West								0
	Central	**1**				1		1	3
	East						1	1	2

* West (Saskatchewan, Manitoba); Central (Ontario, Quebec); East (Prince Edward Island, Nova Scotia, New Brunswick, Newfoundland and Labrador).

Proportion of SAVE Isolates Contained in PCV-13

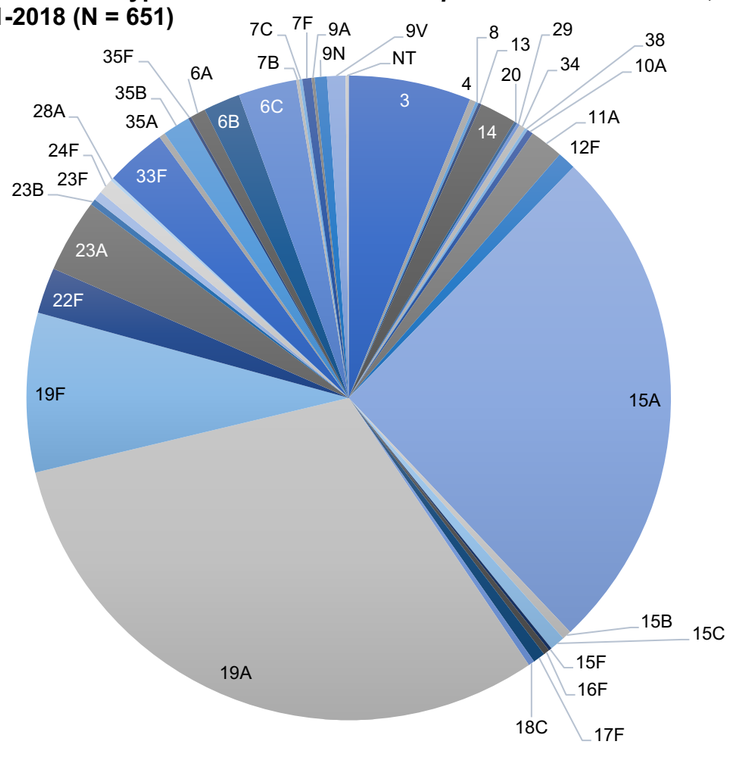
In 2018, 28.0% of the *S. pneumoniae* collected as part of SAVE were serotypes contained in PCV-13. Regional variation of serotypes was noted as 19.3%, 31.0% and 22.7% of the isolates were PCV-13 serotypes in the West, Central and Eastern parts of Canada, respectively. Variability in the proportion of *S. pneumoniae* contained in PCV-13 by age group was also noted: 21.2% in 0-<1 years, 10.6% in 1-<2 years, 32.8% in 2-<6 years, 39.6% in 6-<18 years, 30.6% in 18-<50 years, 32.6% in 50-<65 years and 23.8% in ≥65 years.

Multidrug Resistance

Current (2018) MDR was noted in serotypes 3 (6.0%), 6A/B/C (30/33.3/11.4%), 9N/V (0.9/3.2%), 11A (8.0%), 12F (2.2%), 14 (60%), 15A/B/C (55.8/3.0/6.3%), 17F (6.9%), 19A/F (25/13.6%), 20 (2.0%), 22F (2.4%), 23A/B/F (12.7/2.9/50%), 24F (7.7%), 33F (3.0%), 35B (11.6%) and nontypeable isolates (11.1%). Of the MDR isolates collected, 45.0% (54/120) were PCV-13 serotypes.

Of the 120 MDR *S. pneumoniae* in SAVE 2018, 39 isolates were resistant to 3 antimicrobial classes, 43 resistant to 4 antimicrobial classes, 29 were resistant to 5 antimicrobial classes and 9 were resistant to 6 antimicrobial classes. The most common MDR phenotype demonstrated resistance to chloramphenicol, clarithromycin, clindamycin, and doxycycline (n=34; predominantly serotypes 3, n=14 and 15A, n=12).

Figure 1. Serotype Distribution of MDR *S. pneumoniae* in Canada, 2011-2018 (N = 651)



Conclusions

1. In 2018, 28.0% of all circulating *S. pneumoniae* and 45.0% of MDR *S. pneumoniae* in Canada were serotypes in PCV-13.
2. The most commonly circulating serotypes in the 2018 SAVE study were 3, 22F, 8, 9N, 19A, 12F, 11A, 15A, 23B and 33F.
3. Rates of multidrug resistance in *S. pneumoniae* demonstrated a decreasing trend between 2011 and 2018, however it was not quite statistically significant (*P*=0.057).
4. In 2018, multidrug resistance was observed in serotypes 3, 6A/B/C, 9N/V, 11A, 12F, 14, 15A/B/C, 17F, 19A/F, 20, 22F, 23A/B/F, 24F, 33F, 35B and nontypeable isolates. The most common MDR phenotype demonstrated resistance to chloramphenicol, clarithromycin, clindamycin and doxycycline.
5. In the overall SAVE 2011-2018 study, 651 MDR *S. pneumoniae* have been collected. The majority of the MDR *S. pneumoniae* are serotypes 15A (25.7%) and 19A (30.7%).