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Antimicrobial Susceptibility Patterns of Common Invasive *Streptococcus pneumoniae* Serotypes in Canada: SAVE 2011-2020

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Introduction

The introduction of Prevnar® (PCV7), 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-PCV7 *S. pneumoniae* serotypes in Canada, particularly multidrug-resistant (MDR) strains was of significant concern. Subsequently, newer pneumococcal conjugate vaccines were developed with enhanced serotype coverage, including Prevnar®13 (PCV13). The broader serotype coverage and critical inclusion of serotype 19A in PCV13 offers an important advancement in the protection of Canadian children against invasive *S. pneumoniae* infections. Current immunization guidelines recommend the routine use of PCV13 in Canada [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 PCV13 vaccine. Changes in serotype distribution and multidrug resistance rates between 2011 and 2020 were assessed to evaluate the evolution of serotypes and antimicrobial resistance subsequent to the introduction of PCV13 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 Public Health Agency of Canada – National Microbiology Laboratory (PHAC-NML). Through a collaboration between the Canadian Antimicrobial Resistance Alliance (CARA) and PHAC-NML, 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 14,138 invasive *S. pneumoniae* isolates from across Canada were included in the SAVE study as part of this collaboration (Jan. 1, 2011 – Dec. 31, 2020) with 1073 collected in 2020.

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing was performed using custom designed in-house manufactured antimicrobial susceptibility panels using CLSI methods [4]. MICs were determined by the broth microdilution method and interpreted utilizing CLSI criteria [4,5]. MDR-isolates were defined as resistant 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 serotypes and rates of MDR-*S. pneumoniae* throughout the study were assessed for statistical significance using the Cochran-Armitage test.

Results

Proportion of SAVE Isolates Contained in PCV13

In 2020, 33.6% of the *S. pneumoniae* collected as part of SAVE were serotypes contained in PCV13. Slight regional variation of serotypes was noted as 40.4%, 32.0% and 22.1% of the isolates were PCV13 serotypes in the West, Central and Eastern parts of Canada, respectively. Variability in the proportion of *S. pneumoniae* contained in PCV13 by age group was also noted: 36.8% in 0-<1 year, 17.6% in 1-<2 years, 29.2% in 2-<6 years, 18.8% in 6-<18 years, 44.2% in 18-<50 years, 37.2% in 50-<65 years and 22.4% in ≥65 years.

Multidrug Resistance

In 2020, multidrug resistance was noted in the following serotypes (% of serotype isolates demonstrating MDR patterns): 3 (3.5%), 4 (11.1%), 7C (7.1%), 9N/V (2.7/14.3%), 11A (3%), 12F (25.5%), 13 (66.7%), 14 (80.0%), 15A (64.3%), 18C (10.0%), 19A/F (37.8/25.0%), 20 (2.2%), 22F (4.5%), 23A (14.3%), 33F (6.1%), 34 (7.7%), 35B/D (10.3/66.7%). Of the MDR-isolates collected, 45.5% (45/99) were PCV13 serotypes.

Of the 99 MDR-*S. pneumoniae* in SAVE 2020, 51 (51.5%) isolates were resistant to 3 antimicrobial classes, 34 (34.3%) were resistant to 4 antimicrobial classes, 13 (13.1%) were resistant to 5 antimicrobial classes and 1 (1.0%) was resistant to 6 antimicrobial classes. The most common MDR phenotype demonstrated resistance to clarithromycin, clindamycin, and doxycycline (n=24; predominantly serotype 15A, n=12).

Acknowledgements

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Results

Table 1. Antimicrobial susceptibilities of the ten most commonly collected serotypes, PCV13 serotypes and all isolates of *S. pneumoniae* collected in SAVE 2020

Serotype (N*)	% Susceptible								% MDR
	PEN (iv, M)	PEN (iv, NM)	CRO (M)	CRO (NM)	CLR	LVX	SXT	DOX	
4 (135/ 135)	99.3	100	100	100	85.9	100	98.5	86.7	11.1
3 (115/ 115)	100	100	100	100	90.4	100	94.8	89.6	3.5
8 (87/ 85)	98.8	100	100	100	100	100	98.8	98.8	0
9N (75/ 75)	97.3	100	100	100	97.3	100	93.3	96.0	2.7
22F (66/ 66)	98.5	98.5	98.5	98.5	50.0	100	93.9	95.5	4.5
12F (55/ 55)	98.2	100	100	100	49.1	100	65.5	63.6	25.5
20 (46/ 46)	100	100	100	100	95.7	100	91.3	93.5	2.2
15A (40/ 28)	28.5	100	82.1	100	25.0	100	96.4	25.0	64.3
19A (37/ 37)	59.5	70.3	70.3	91.9	37.8	100	62.2	62.2	37.8
33F (33/ 33)	100	100	100	100	15.2	100	18.2	90.9	6.1
PCV13 (360/ 360)	92.5	96.1	95.6	98.9	81.1	100	89.2	85.3	11.5
All SPN (1073/ 1048)	90.1	98.6	96.9	99.5	76.7	99.9	85.6	88.4	9.4

M, meningitis; NM, nonmeningitis; PEN, penicillin; CRO, ceftriaxone; CLR, clarithromycin; LVX, levofloxacin; SXT, trimethoprim-sulfamethoxazole; DOX, doxycycline.
*N isolated / N with complete susceptibility data

Table 2. Annual rate of MDR-*S. pneumoniae* (SAVE 2011-2020)

Study Year	N[a]	% MDR
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	1882	6.5
2019	1849	7.6
2020	1048	9.4
P-value (2011-2020)		0.11

[a] N for which complete susceptibility testing data available

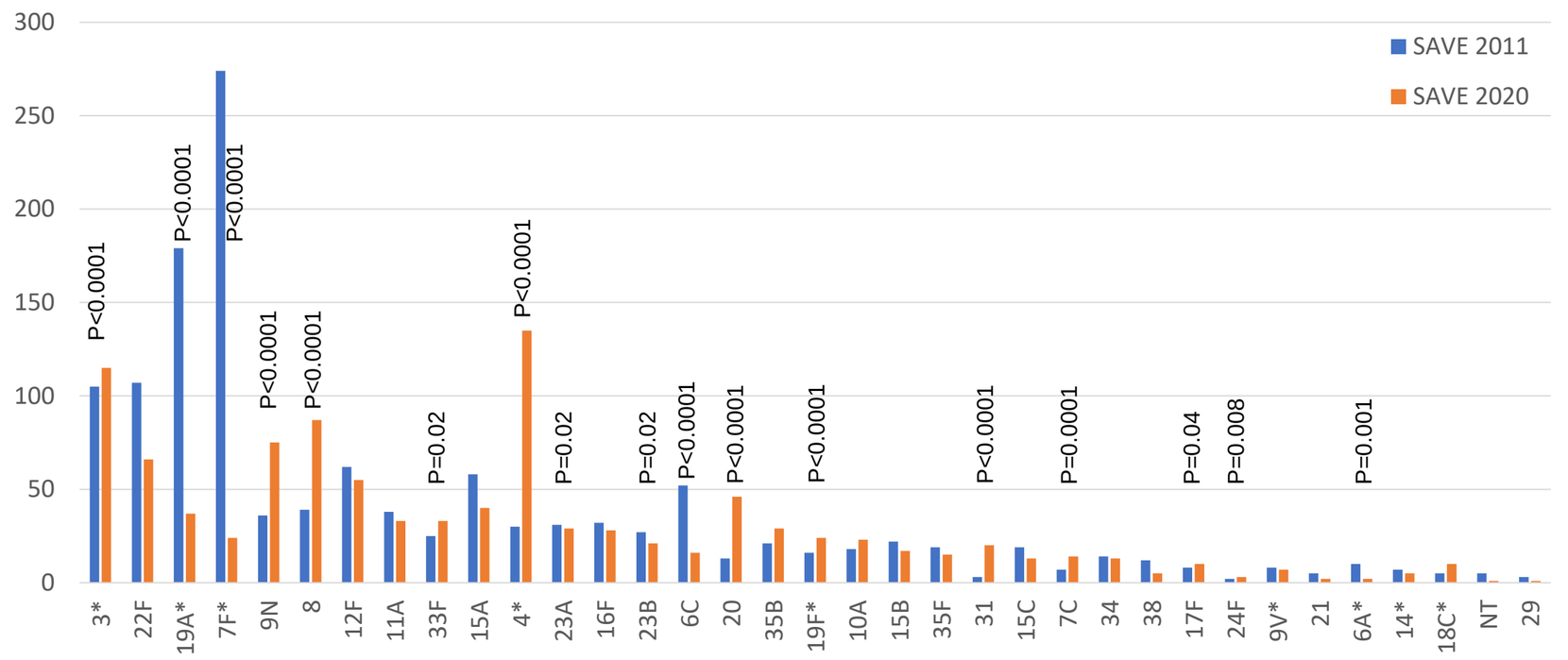

Figure 1. *S. pneumoniae* serotype distribution in 2020 compared to 2011 (for serotypes with ≥50 in total)

Table 3. Demographics of the common (N≥5) MDR-*S. pneumoniae* serotypes in Canada (2020)

Serotype (N)	Region[a]	Age Group (years)							Region Total
		0-<1	1-<2	2-<6	6-<18	18-<50	50-<65	≥65	
15A (18)	West					3	2		5
	Central	1		1			5	3	10
	East							2	2[b]
4 (15)	West								0
	Central	1				4	6	3	14[b]
	East								0
12F (14)	West								0
	Central					6	6	2	14
	East								0
19A (14)	West						3	2	5
	Central	1		1			2	4	8
	East						1		1
19F (6)	West		1						1
	Central	2				2		1	5
	East								0

[a]West (Saskatchewan, Manitoba); Central (Ontario, Quebec); East (Prince Edward Island, Nova Scotia, New Brunswick, Newfoundland and Labrador).
[b]Patient age unknown for 1 MDR serotype 15A and 1 MDR serotype 4 isolate.

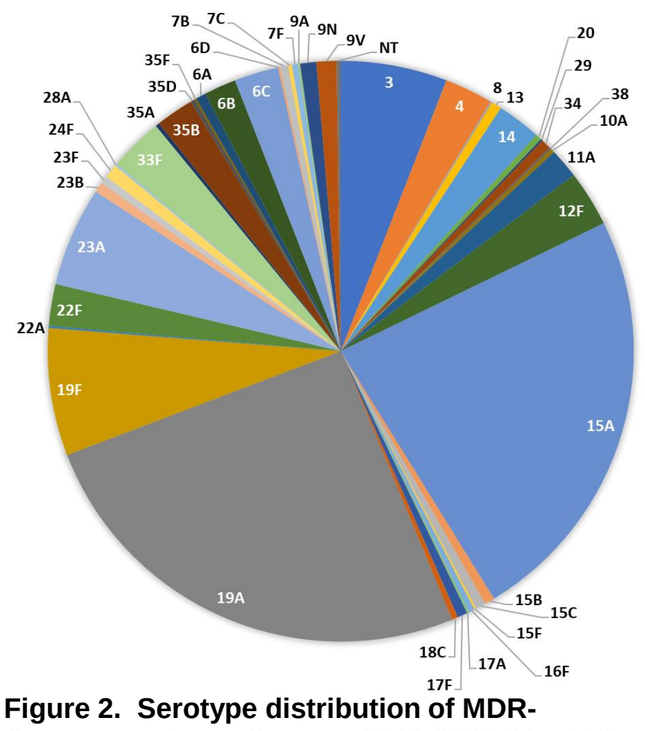

Figure 2. Serotype distribution of MDR-*S. pneumoniae* in Canada, 2011-2020 (N = 902)

Conclusions

1. In 2020, 33.6% of all circulating *S. pneumoniae* and 45.5% of MDR *S. pneumoniae* in Canada were serotypes in PCV13, in comparison to 48.0% and 54.3% in 2011.
2. The most commonly circulating serotypes in the SAVE 2020 study were 4, 3, 8, 9N, 22F, 12F, 20, 15A, 19A and 33F.
3. Between 2011 and 2020, statistically significant reductions in the prevalence of 5, 6A/C, 7F, 19A, 23F, 33A, and 37 were observed.
4. Serotypes 3, 4, 7C, 8, 9N, 17F, 19F, 20, 23A/B, 24A, 31, 33F and 35D demonstrated increasing trends throughout the study. As PCV13 serotypes, the increased prevalence of serotypes 3, 4 and 19F is notable. Serotypes 3 and 4 were the most commonly identified serotypes in 2020. The vaccine effectiveness of serotype 3 is lower than the other serotypes in PCV13 [6]. The SAVE study does not collect any patient-specific information beyond age and gender; accordingly, the vaccine status of these patients is unknown and further conclusions cannot be made.
5. Rates of MDR in *S. pneumoniae* did not significantly change over the study period (2011-2020).
6. In 2020, the serotypes with the highest MDR rates (>50% of isolates) included 13, 14, 15A, 19A, and 35D. Serotypes 13, 14 and 35D were infrequently identified (n≤5).
7. In the overall SAVE 2011-2020 study, 902 MDR *S. pneumoniae* have been collected. The majority of the MDR *S. pneumoniae* are serotypes 15A (23.5%) and 19A (25.4%).