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Antimicrobial Susceptibility Patterns of Common Invasive *Streptococcus pneumoniae* Serotypes in Canada: SAVE 2011 - 2017

H.J. ADAM[1,2], A.R. GOLDEN[1], M. BAXTER[1], I. MARTIN[3], K.A. NICHOL[2], W. DEMCZUK[3], M. MULVEY[3], J.A. KARLOWSKY[1,2], G.G. ZHANEL[1], and the CANADIAN ANTIMICROBIAL RESISTANCE ALLIANCE (CARA)

[1]University of Manitoba, [2]Shared Health and [3]National Microbiology Laboratory, Winnipeg, Manitoba, Canada

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University of Manitoba

Heather Adam
Microbiology, Health Sciences Centre
MS675F-820 Sherbrook St.
Winnipeg, MB R3A 1R9
Email: hadam@sharedhealthmb.ca

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 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 multidrug resistance (MDR) rates between 2011 and 2017 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 9166 invasive *S. pneumoniae* isolates from across Canada were included in the SAVE study as part of this collaboration (Jan. 1, 2011 – Dec. 31, 2017) with 1544 collected in 2017.

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing was performed using custom designed in-house manufactured antimicrobial susceptibility panels using CLSI methods. 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 (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 identified serotypes and MDR rates throughout the study were assessed for statistical significance using the Cochran-Armitage test.

Results

Table 1. Antimicrobial Susceptibilities for the Top 10 Serotypes of *S. pneumoniae* in SAVE 2017

Serotype (N)	% Susceptible								% MDR
	PEN (iv, M)	PEN (iv, NM)	CRO (M)	CRO (NM)	CLR	LVX	SXT	DOX	
3 (149)	97.3	100	99.3	100	91.9	100	97.3	85.1	6.8
22F (135)	99.3	100	100	100	74.8	100	99.3	99.3	2.2
9N (101)	93.1	100	100	100	90.1	100	93.1	96.0	2
23A (78)	61.0	100	98.7	100	72.7	100	94.8	68.8	15.6
19A (78)	75.6	93.6	93.6	97.4	51.3	100	78.2	78.2	16.7
8 (73)	100	100	100	100	98.6	100	100	97.3	0
33F (73)	100	100	100	100	38.4	100	20.5	93.2	5.5
12F (73)	100	100	100	100	43.8	100	100	100	0
15A (63)	34.1	100	90.9	100	29.5	95.5	88.6	36.4	59.1
19F (62)	70.5	91.8	83.6	93.4	72.1	95.1	82.0	72.1	26.2

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)]

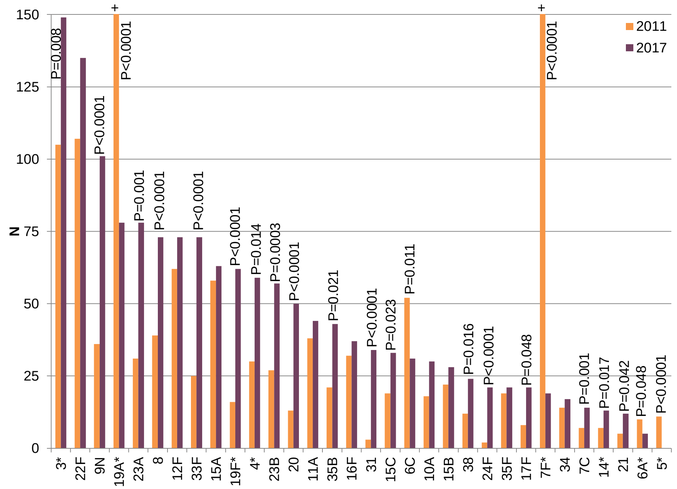

Figure 1. *S. pneumoniae* Serotype Distribution in 2017 compared to 2011 (for serotypes with ≥10 in either year)

*, PCV-13 Serotypes; +, 19A N=179 in 2011, 7F N=274 in 2011; Statistical significance reflects trends over the whole study (2011 – 2017) while the data shown only portrays the end point years of 2011 and 2017. Although greater numbers of serotypes 4 and 9V were isolated in 2017 compared to 2011, the serotypes showed a decreasing trend when all study years were evaluated.

Table 2. Annual Prevalence of MDR in *S. pneumoniae* in Canada, 2011-2017

	SAVE Study Year							P-value, 2011 to 2017
	2011	2012	2013	2014	2015	2016	2017	
***S. pneumoniae* isolates (N)**	1379	1285	1138	1210	1196	1208	1544	N/A
MDR Rate	8.5%	6.8%	5.9%	3.9%	5.7%	3.9%	6.7%	P=0.002

N/A, not applicable

Table 3. Demographics of the Common (N≥5) MDR *S. pneumoniae* by Serotype in Canada (2017)

Serotype (N)	Geographic Region *	Age Group (years)							Region Total
		0-<1	1-<2	2-<6	6-<18	18-<50	50-<65	≥65	
15A (26)	West						2	2	4
	Central		1			1	3	11	16
	East				1	1		4	6
19F (16)	West						4	1	5
	Central					4	5	2	11
	East								0
19A (13)	West					2	1	1	4
	Central			2			2	3	7
	East							2	2
23A (12)	West								
	Central						3	5	8**
	East			1				1	2
3 (10)	West							2	2
	Central					1	5	2	8
	East								0

* West (Saskatchewan, Manitoba); Central (Ontario, Quebec); East (Prince Edward Island, Nova Scotia, New Brunswick, Newfoundland and Labrador); **, Patient age unknown for 2 MDR serotype 23A isolates

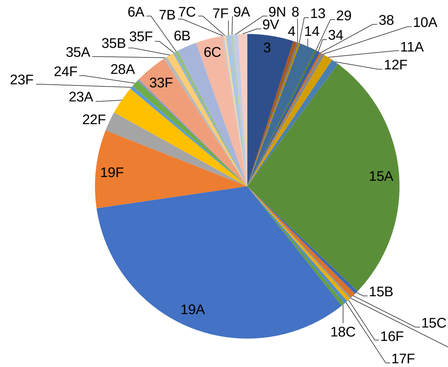

Figure 2. Serotype Distribution of MDR *S. pneumoniae* in Canada, 2011-2017 (N = 531)

Proportion of SAVE Isolates Contained in PCV-13

In 2017, 26.2% of the *S. pneumoniae* collected as part of SAVE were serotypes contained in PCV-13. Regional variation of serotypes was noted as 13.0%, 31.3% and 19.2% 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: 11.1% in 0-<1 years, 7.7% in 1-<2 years, 24.7% in 2-<6 years, 33.3% in 6-<18 years, 30.9% in 18-<50 years, 31.6% in 50-<65 years and 22.9% in ≥65 years.

Antimicrobial Susceptibility Rates

The antimicrobial susceptibility rates for all *S. pneumoniae* and PCV-13 serotypes in 2017 was as follows: penicillin (iv, nonmeningitis) 99.2% and 97%, penicillin (iv, meningitis and oral) 86% and 84.5%, ceftriaxone (nonmeningitis) 99.4% and 98%, ceftriaxone (meningitis) 97.8% and 94%, clarithromycin 78.3% and 80%, levofloxacin 99.5% and 99%, trimethoprim-sulfamethoxazole 85.5% and 85%, and doxycycline 89.9% and 83.3%.

Multidrug Resistance

Current (2017) MDR was noted in serotypes 3 (6.8%), 4 (1.7%), 6A/B/C (20/25/3.2%), 7B/C (50/7.1%), 9N (2%), 11A (4.5%), 14 (15.4%), 15A (59.1%), 16F (2.9%), 18C (14.3%), 19A/F (16.7/26.2%), 22F (2.2%), 23A (15.6%), 24F (11.1%), 33F (5.5%) and 35F (4.8%).

Of the 101 MDR *S. pneumoniae* in SAVE 2017, 50 isolates were resistant to 3 antibiotic classes, 32 resistant to 4 antibiotic classes, 14 were resistant to 5 antibiotic classes and 5 were resistant to 6 antibiotic classes. The most common MDR phenotype demonstrated resistance to clarithromycin, clindamycin, and doxycycline (n=41; predominantly serotypes 15A, n=15 and 23A, n=11).

Conclusions

1. In 2017, 26.2% of all circulating *S. pneumoniae* and 44.6% of MDR *S. pneumoniae* in Canada were serotypes in PCV-13.
2. The most commonly circulating serotypes in the 2017 SAVE study were 3, 22F, 9N, 8, 23A, 19A, 8, 33F, 12F, 15A and 19F.
3. Between 2011 and 2017, statistically significant reductions in the prevalence of 1, 4, 5, 6A, 6C, 7F, and 19A were observed.
4. Serotypes 3, 7C, 8, 9N, 14, 15C, 17F, 19F, 20, 21, 23A, 23B, 24F, 31, 33F and 38 demonstrated increasing trends throughout the study. As PCV-13 serotypes, the increased prevalence of serotypes 3, 14, and 19F is notable. The vaccine effectiveness of serotype 3 is lower than the other serotypes in PCV-13 (7). Serotype 14 was infrequently isolated in Canada despite the increasing prevalence representing only 45 of 9166 isolates in the SAVE study. 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. In 2017, multidrug resistance was observed in serotypes 3, 4, 6A/B/C, 7B/C, 9N, 11A, 14, 15A, 16F, 18C, 19A, 19F, 22F, 23A, 24F, 33F, 35F.
6. Rates of multidrug resistance in *S. pneumoniae* demonstrated a decreasing trend between 2011 and 2017 (P=0.002).
7. Overall, 531 MDR *S. pneumoniae* have been collected. The majority of the MDR *S. pneumoniae* are serotypes 15A (26.9%) and 19A (33.3%).
8. The change in serotype distribution, specifically the decreased prevalence of 19A, subsequent to the introduction of PCV13 may account for the decreased rate of MDR in *S. pneumoniae* in Canada.

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