

The 13-valent Pneumococcal Conjugate Vaccine Provides Excellent Coverage of Multi-drug Resistant *Streptococcus pneumoniae* in Canada

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ABSTRACT

Background: The serotypes of *S. pneumoniae* circulating in Canada prior to the introduction of PCV-13 were assessed in the Baseline Epidemiology of *Streptococcus pneumoniae* Serotypes (BESST) study. **Methods:** 800 *S. pneumoniae* obtained from blood cultures and respiratory specimens as part of CANWARD (an annual national surveillance study) between 2007 and 2009, inclusive were serotyped by the Quellung method and susceptibility testing was performed with CLSI methodology. **Results:** Forty-eight different serotypes were observed. The most common serotypes were 19A (9%), 3 (7%), 22F (6%), 4 (5%), and 5 (4%). Among children ≤ 2 years, serotypes 19A (23%) and 15B (10%) predominated. Overall, 46%, 28%, and 20% of the strains belonged to PCV-13, PCV-10, and PCV-7 serotypes, respectively ($P < 0.001$, PCV-13 vs PCV-7). Among blood culture isolates, 54%, 56%, 71%, 52%, and 52% of strains belonged to PCV-13 (overall, ≤ 2 , 3-16, 17-49, and ≥ 50 years, respectively). Selected antimicrobial susceptibilities are portrayed in the table below by PCV-13 serotype coverage. Antimicrobial Agent (CLSI interpretative criteria)

	% Susceptible (All Blood/ Respiratory)	
	PCV-13 serotypes	Non-PCV-13 serotypes
Penicillin (meningitis)	74/79/68	87/83/90
Penicillin (nonmeningitis)	98/99/97	100/100/100
Ceftriaxone (meningitis)	97/99/95	100/100/100
Ceftriaxone (nonmeningitis)	99/100/99	100/100/100
Clarithromycin	79/86/69	92/94/90
Levofloxacin	100/100/99	100/100/100
Trimethoprim-sulfamethoxazole	79/84/73	94/92/96
Doxycycline (interpreted with tetracycline breakpoints)	93/96/90	97/100/94

Multi-drug resistance (MDR, ≥ 3 antimicrobial classes) was observed with serotypes 9V (6%), 15A (5%), 19A (9%), 19F (6%), 22F (2%), and 23F (11%). 88% of the MDR isolates were PCV-13 serotypes. **Conclusion:** The BESST study demonstrates that PCV-13 will provide good coverage of the circulating *S. pneumoniae* strains in Canada. Importantly, PCV-13 serotypes encompass the majority of antimicrobial non-susceptible *S. pneumoniae* in Canada.

BACKGROUND

In the early 2000s, pneumococcal conjugate vaccines were approved for use and included in the routine infant immunization schedules in Canada and in the United States. A seven-valent formulation (PCV-7) was the first approved pneumococcal conjugate vaccine. The 7 serotypes included in PCV-7 (4, 6B, 9V, 14, 18C, 19F, 23F) accounted for more than 80% of invasive pneumococcal disease (IPD) in North American children at that time [1].

Dramatic decreases in the incidence of IPD were observed subsequent to the introduction of PCV-7, particularly in young children but also in individuals 5 years of age and older, demonstrating considerable herd immunity [1, 2]. Despite the success of PCV-7, the incidence of IPD caused by non-PCV-7 serotypes subsequently increased, particularly due to 19A strains [3].

In order to enhance the protection provided by the pneumococcal conjugate vaccines, new formulations have been developed including the 10-valent vaccine (PHiD-CV), composed of the PCV-7 serotypes plus 1, 5, and 7F, and the 13-valent vaccine (PCV-13), composed of the PHiD-CV serotypes plus 3, 6A, and notably 19A.

The purpose of this study was to assess the circulating serotypes of *S. pneumoniae* from all age groups in Canada between 2007 and 2009, prior to the introduction of PCV-13.

MATERIALS & METHODS

Bacterial Isolates. *S. pneumoniae* isolates were collected as part of the CANWARD study (an annual national surveillance study) from patients in 15 tertiary-care centres across Canada between 2007 and 2009, inclusive [4]. Eight hundred isolates (400 respiratory isolates and 400 blood culture isolates) were randomly selected for this study.

Antimicrobial Susceptibility Testing. Antimicrobial susceptibility testing was performed using the broth microdilution method recommended by the Clinical and Laboratory Standards Institute [5]. Custom-designed broth microdilution panels were prepared in-house with cation-adjusted Mueller-Hinton broth with 5% laked horse blood and antimicrobial agents obtained as laboratory-grade powders from their respective manufacturers or from Sigma-Aldrich (Oakville, Canada), as required. The minimum inhibitory concentrations (MICs) were interpreted based on CLSI M100-S21 breakpoints.

Serotype Determination. The serotype of each isolate was determined by the Quellung reaction following standard methodology [6] using type specific antisera obtained from the Statens Serum Institut (Copenhagen, Denmark). Infrequently observed serotypes were confirmed at the National Microbiology Laboratory – Public Health Agency of Canada.

Statistical Analysis. Statistical significance was evaluated by two-tailed Chi-squared analysis or Fisher's exact test, as appropriate.

RESULTS

Figure 1. Serotype distribution of 800 *S. pneumoniae* in Canada by age group (≤ 2 years, 3 to 16 years, 17 to 49 years, and ≥ 50 years) collected between 2007 and 2009

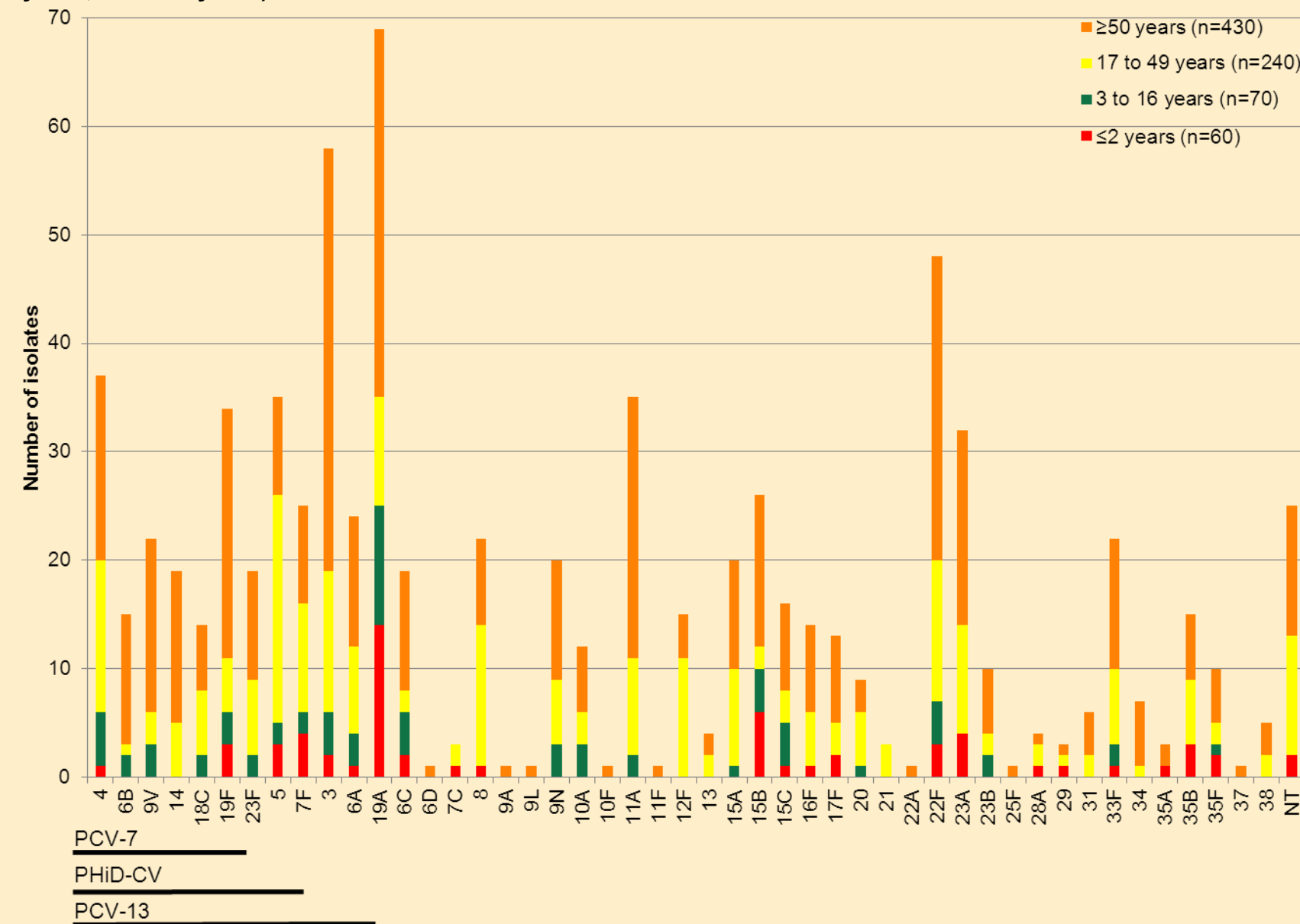


Table 2. Antimicrobial susceptibility of *S. pneumoniae* isolates from 2007-2009 in Canada stratified by PCV-13 coverage and specimen source

Antimicrobial Agent (CLSI interpretative criteria)	Specimen Source	% Susceptible			
		All Serotypes (n=800)	PCV-13 Serotypes (n=371)	PCV-13-related Serotypes (n=87)	Non-PCV-13 Serotypes (n=342)
Penicillin (iv, meningitis)	All	80.8	74	87.4	86.1
	Blood	85.9	79.1	83.3	95.8
	Respiratory	76	67.5	90.2	79
Penicillin (iv, nonmeningitis)	All	98.6	97.7	100	99.1
	Blood	99.2	98.5	100	100
	Respiratory	98	96.8	100	98.5
Ceftriaxone (meningitis)	All	98.1	96.6	100	99.1
	Blood	99.5	99	100	100
	Respiratory	97.5	94.7	100	99
Ceftriaxone (nonmeningitis)	All	99.5	99.4	100	99.4
	Blood	100	100	100	100
	Respiratory	99	98.7	100	99
Clarithromycin	All	80.8	78.8	91.8	80.2
	Blood	87.2	86.2	94.3	86.7
	Respiratory	74.6	68.6	90	75.4
Levofloxacin	All	99.2	99.7	100	98.5
	Blood	100	100	100	100
	Respiratory	98.5	99.4	100	97.4
Trimethoprim-Sulfamethoxazole	All	85.9	79.1	94.3	90.8
	Blood	88.7	83.6	91.7	95.1
	Respiratory	83.2	73.2	96.1	87.7
Doxycycline (interpreted with tetracycline breakpoints)	All	93.5	93.4	96.5	92.9
	Blood	95.4	95.9	100	93.7
	Respiratory	91.7	90.2	94	92.3

Table 1. Serotype coverage of PCV-13, PHiD-CV and PCV-7 against current *S. pneumoniae* serotypes in Canada

Specimen source	Age group	Serotype categorization	Vaccine			P value, PCV-13 vs PCV-7			
			PCV-13	PHiD-CV	PCV-7				
All isolates (n=800)		Vaccine serotypes	371	46.4	220	27.5	160	20	<0.001
		Vaccine-related serotypes	87	10.9	180	22.5	177	22.1	<0.001
		Non-vaccine serotypes	342	42.8	400	50	463	57.9	<0.001
≤ 2 years (n=60)		Vaccine serotypes	28	46.7	11	18.3	4	6.7	<0.001
		Vaccine-related serotypes	7	11.7	22	36.7	21	35	0.005
		Non-vaccine serotypes	25	41.7	27	45	35	58.3	0.1
3 – 16 years (n=70)		Vaccine serotypes	39	55.7	21	30	17	24.3	<0.001
		Vaccine-related serotypes	9	12.9	23	32.9	23	32.9	0.008
		Non-vaccine serotypes	22	31.4	26	37.1	30	42.9	0.2
17 – 49 years (n=240)		Vaccine serotypes	103	42.9	72	30	41	17.1	<0.001
		Vaccine-related serotypes	22	9.2	40	16.7	38	15.8	0.04
		Non-vaccine serotypes	115	47.9	128	53.3	161	67.1	<0.001
≥ 50 years (n=430)		Vaccine serotypes	201	46.7	116	27	98	22.8	<0.001
		Vaccine-related serotypes	49	11.4	95	22.1	95	22.1	<0.001
		Non-vaccine serotypes	180	41.9	219	50.9	237	55.1	<0.001
Blood isolates (n=400)		Vaccine serotypes	217	54.3	131	32.8	76	19	<0.001
		Vaccine-related serotypes	36	9	92	23	92	23	<0.001
		Non-vaccine serotypes	147	36.8	177	44.3	232	58	<0.001
≤ 2 years (n=41)		Vaccine serotypes	23	56.1	9	22	3	7.3	<0.001
		Vaccine-related serotypes	2	4.9	14	34.1	14	34.1	0.02
		Non-vaccine serotypes	16	39	18	43.9	24	58.5	0.08
3 – 16 years (n=38)		Vaccine serotypes	27	71.1	15	39.5	11	28.9	<0.001
		Vaccine-related serotypes	2	5.3	12	31.6	12	31.6	0.006
		Non-vaccine serotypes	9	23.7	11	28.9	15	39.5	0.1
17 – 49 years (n=122)		Vaccine serotypes	64	52.5	51	41.8	21	17.2	<0.001
		Vaccine-related serotypes	10	8.2	17	13.9	17	13.9%	0.2
		Non-vaccine serotypes	48	39.3	54	44.3	84	68.9	<0.001
≥ 50 years (n=199)		Vaccine serotypes	103	51.8	56	28.1	41	20.6	<0.001
		Vaccine-related serotypes	22	11	49	24.6	49	24.6	<0.001
		Non-vaccine serotypes	74	37.2	94	47.2	109	54.8	0.4
Respiratory isolates (n=400)		Vaccine serotypes	154	38.5	89	22.3	84	21	<0.001
		Vaccine-related serotypes	51	12.8	88	22	85	21.3	0.02
		Non-vaccine serotypes	195	48.8	223	55.8	231	57.8	0.01
≤ 2 years (n=19)		Vaccine serotypes	5	26.3	2	10.5	1	5.3	0.2
		Vaccine-related serotypes	5	26.3	8	42.1	7	36.8	0.5
		Non-vaccine serotypes	9	47.4	9	47.4	11	57.9	0.5
3 – 16 years (n=32)		Vaccine serotypes	12	37.5	6	18.8	6	18.8	0.1
		Vaccine-related serotypes	7	21.9	11	34.4	11	34.4	0.3
		Non-vaccine serotypes	13	40.6	15	46.9	15	46.9	0.6
17 – 49 years (n=118)		Vaccine serotypes	39	33.1	21	17.8	20	16.9	0.004
		Vaccine-related serotypes	12	10.2	23	19.5	21	17.8	0.09
		Non-vaccine serotypes	67	56.8	74	62.7	77	65.3	0.2
≥ 50 years (n=231)		Vaccine serotypes	98	42.4	60	26.0	57	24.7	<0.001
		Vaccine-related serotypes	27	11.7	46	19.9	46	19.9	0.02
		Non-vaccine serotypes	106	45.9	125	54.1	128	55.4	0.04

Table 3. Antimicrobial susceptibility of *S. pneumoniae* isolates with serotypes included in PCV-13 and common non-vaccine serotypes (n ≥ 20) from CANWARD 2007-2009

Serotype (n ^a)	% Susceptible								
	Clari	Levo	Pen (Non-men)	Pen (Men)	CTR (Non-men)	CTR (Men)	TMP-SMX	Doxy	MDR 2/2 ^b
3 (n=48)	93.8	100	100	97.9	100	100	100	97.9	0/0
4 (n=37)	89.2	100	100	100	100	100	100	97.3	0/0
5 (n=35)	100	100	100	94.3	100	100	100	70.6	0/0
6A (n=24)	52.2	100	100	41.7	100	100	100	78.3	0/0
6B (n=15)	60	100	100	80	100	100	100	66.7	0/0
7F (n=21)	100	100	100	100	100	100	100	100	0/0
9V (n=22)	100	100	100	100	100	100	100	100	0/0
9N (n=20)	100	100	100	100	100	100	100	100	0/0
11A (n=16)	87.5	100	87.5	12.5	100	93.8	6.25	100	43.8/6.3
11A (n=34)	82.4	97.1	100	97.1	100	100	94.1	97.1	0/0
14 (n=19)	52.6	94.7	100	73.7	100	84.2	84.2	89.5	10.5/0
15A (n=20)	40	100	95	60	100	100	100	40	0/5
15B (n=24)	66.7	100	100	87.5	100	100	91.7	100	0/0
18C (n=14)	100	100	100	100	100	100	85.7	100	0/0
19A (n=68)	61.8	100	92.6	50	98.5	95.6	69.6	83.8	0/8.8
19F (n=35)	79.4	100	100	67.6	97.1	91.2	82.4	79.4	2.9/5.7
22F (n=48)	93.8	100	97.9	95.8	97.9	97.9	95.8	100	0/2.1
23A (n=32)	93.3	100	100	75	100	100	96.9	90	0/0
23F (n=19)	68.4	100	94.7	63.2	100	89.5	63.2	100	0/10.5
33F (n=22)	72.7	100	100	90.9	100	100	59.1	100	0/0
NT (n=25)	48	84	96	36	100	96	64	68	4/0

^a with complete susceptibility testing results; ^bMDR 2, multi-drug resistant to 2 drug classes (penicillin (Pen) MIC ≥ 2 µg/mL + clarithromycin (Clari) or levofloxacin (Levo) or trimethoprim-sulfamethoxazole (TMP-SMX) or doxycycline (Doxy) resistance); MDR₃, multi-drug resistant ≥ 3 drug classes (Pen MIC ≥ 2 µg/mL + resistance to 2 or more of Clari / Levo / TMP-SMX / Doxy); Non-men, non-meningitis; Men, meningitis

CONCLUSIONS

The most common serotypes circulating in Canada are 19A, 3, 22F, 4, 5, and 11A. Serotypes 5, 7F, and 19A were isolated significantly more frequently from bloodstream infections than respiratory specimens ($P < 0.001$). Conversely, serotypes 6A ($P = 0.04$), 19F ($P = 0.04$), 23F ($P = 0.02$) and non-typeable isolates ($P < 0.001$) were more commonly observed from respiratory specimens.