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Streptococcus pneumoniae serotype 3 is masking PCV13-mediated herd immunity in Canadian adults hospitalized with community acquired pneumonia: A study from the Serious Outcomes Surveillance (SOS) Network of the Canadian immunization research Network (CIRN)

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ABSTRACT

Background: The 13-valent pneumococcal conjugate vaccine (PCV13) was recently shown to be effective against PCV13-type invasive pneumococcal disease (IPD) and pneumococcal community acquired pneumonia (CAP_{Spn}) in healthy adults aged ≥65 years, prompting many countries to re-assess adult immunization. In Canada, the potential benefits of adult PCV13 immunization were unclear given anticipated herd immunity from PCV13 childhood immunization introduced since 2010. This study describes the serotype distribution and clinical outcomes of Canadian adults aged ≥16 years, who were hospitalized with CAP_{Spn} and IPD from 2010 to 2015.

Methods: Active surveillance for CAP and IPD was performed in adult hospitals across five Canadian provinces. IPD was identified when *Streptococcus pneumoniae* was isolated from sterile sites. Bacteremic and non-bacteremic CAP_{Spn} were identified using blood culture, and sputum culture or PCV13-specific urine antigen detection (UAD_{PCV13}), respectively. Serotype was assigned using Quellung reaction, PCR, or UAD_{PCV13}.

Results: Of 6687 CAP cases where a test was performed, *S. pneumoniae* positivity decreased from 15.9% in 2011 to 8.8% in 2014, but increased to 12.9% in 2015. CAP_{Spn} attributed to PCV13 serotypes followed a similar trend, dropping from 8.3% in 2010 to 4.6% in 2014, but increasing to 6.3% in 2015. The decline was primarily attributed to serotypes 7F and 19A, and the proportional increase to serotype 3. Similar trends were noted for bacteremic and non-bacteremic CAP_{Spn}. Serious outcomes such as 30-day mortality, intensive care unit admission, and requirement for mechanical ventilation were prominent in CAP_{Spn} and IPD cases, but remained unchanged over the study years.

Conclusion: Herd immunity afforded primarily by serotypes 7F and 19A appears to be partly masked by a concomitant proportional increase of serotype 3. Despite evidence of herd immunity, these PCV13

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serotypes remain persistent in Canadian adults hospitalized with CAP_{Spn}, and represent between 5 and 10% of all CAP in this patient population.

1. Introduction

Community acquired pneumonia (CAP) is the leading infectious cause of adult mortality in developed countries, and *Streptococcus pneumoniae* (pneumococcus) is the most frequently associated bacterial pathogen [1–6]. Recent reports in Canada suggest the proportion of CAP attributed to *S. pneumoniae* (CAP_{Spn}) in hospitalized adults can range from 14 to 23%, depending on the diagnostic methods used [1]. Other than CAP_{Spn}, the spectrum of pneumococcal infections ranges from mild upper respiratory tract illness to invasive pneumococcal diseases (IPD). CAP_{Spn} and IPD are significant contributors to morbidity and mortality worldwide, and the incidence is highest in children under 5 years of age, elderly adults, and individuals with underlying co-morbidities [1–6]. *S. pneumoniae* virulence is primarily linked to its polysaccharide capsule, which helps subvert immune defenses, and differences in polysaccharide capsule composition have helped characterize *S. pneumoniae* into over 92 serotypes [7]. Some pneumococcal capsular polysaccharides or protein-polysaccharide conjugates have been used successfully as vaccines targets [7].

In Canada, as in many countries, pneumococcal vaccination is recommended for children and adults at increased risk for pneumococcal disease [8,9]. Due to poor immunological responses to non-conjugated pneumococcal polysaccharide vaccines in children under two years of age, only the conjugated formulations are recommended for childhood immunization [8,9]. Following childhood immunization programs using a 7-valent pneumococcal conjugate vaccine (PCV7), a decline in IPD caused by PCV7-serotypes was observed among vaccinated children, as well as indirect benefits for unvaccinated children and adults through herd immunity [10–16]. Despite these successes, non-PCV7 serotypes like serotype 19A later emerged through serotype replacement [16–19]. By January 2011, the 13-valent conjugate vaccine (PCV13) replaced PCV7 in childhood immunization programs across all Canadian provinces, providing coverage for all PCV7 serotypes in addition to serotypes 1, 3, 5, 6A, 7F, and 19A [8]. Following implementation, the incidence of IPD caused by PCV13 serotypes declined in children, and this was primarily attributed to a reduction in serotypes 7F and 19A [16–18,20–23].

More recently, the CAPiTA trial showed direct immunization with PCV13 to be effective in the prevention of vaccine-type CAP and IPD in immunocompetent adults aged ≥65 years, in the background of a PCV7-based childhood immunization program [24]. In Canada, the potential benefits of PCV13 use in healthy adults was unclear given the anticipated herd immunity from PCV13 childhood immunization [8]. PCV13 was authorized for use in Canadian adults aged ≥50 years for the prevention of IPD since 2012. In 2013, the National Advisory Committee on Immunization (NACI) recommended the use of PCV13 for the prevention of IPD in adults at risk for pneumococcal disease [8]. In 2016, NACI released an interim guidance report updating recommendations for the use of PCV13 in immunocompetent adults aged ≥65 years, on an individual basis, for the prevention of vaccine-type CAP and IPD [8]. NACI deferred recommendations for universal use of PCV13 in immunocompetent adults due to the need to better understand the impact of childhood PCV13 immunization on CAP_{Spn} and IPD in adults.

The Serious Outcomes Surveillance (SOS) Network of the Canadian Immunization Research Network (CIRN) has been conducting active surveillance for CAP and IPD in hospitalized adults since December 2010, the year most provinces introduced PCV13 childhood immunization [1,2]. In a recent publication [1], the clinical outcomes associated with CAP_{Spn} and IPD were described for a three-year period (years 2010–2013) following introduction of childhood PCV13 vaccination. CAP_{Spn} was shown to represent between 14 and 23% of all cause CAP in hospitalized Canadian adults. Most CAP_{Spn} cases (78%) were in adults aged ≥50, and approximately half (47%) were in adults aged ≥65. This supported recent vaccine recommendations for adults aged ≥65 years in Canada [8] and US [9], or in adults aged ≥50 years in Western Europe [25]. Other data from the CIRN SOS Network study showed the proportion of CAP_{Spn} cases attributed to PCV13 serotypes ranged between 7.0% and 14.8%, depending on the methodology used [1]. Herd immunity from childhood PCV13 immunization programs was not evident at the time. The current study uses the same methodology previously described for the period 2010–2013 [1], and provides ongoing surveillance data for 2014 and 2015, enabling assessment of serotype distribution changes over the 2010–2015 period, as well as trends in the burden of CAP_{Spn} and IPD over that time period. Given the anticipated her immunity in adults from childhood PCV13 immunization, the data gathered in hospitalized adults focused on PCV13 serotypes in order to characterize the impact of herd immunity in Canadian adults.

2. Materials and methods

All methods were performed as described previously [1], with the exception of the statistical analyses for proportions comparison during the two different study periods and the trend analyses.

2.1. Study eligibility

This study reports on CAP and IPD cases admitted to hospitals across five Canadian provinces between January 1, 2014 and December 31, 2015, and provided comparisons to previously published data reported by the CIRN SOS Network for the period of December 1, 2010 to December 31, 2013 [1]. Dedicated surveillance monitors reviewed all daily adult admissions (aged ≥16 years) to identify patients with an acute respiratory illness who were admitted to hospitals from the community with an admitting diagnosis of influenza, CAP, asthma or acute exacerbation of chronic obstructive pulmonary disease, or who presented with any other respiratory tract infection or symptom. To identify cases of IPD, laboratory result logs were reviewed for *S. pneumoniae*-positive cultures from normally sterile sites including blood and various fluids (i.e cerebral spinal fluid, pleural, and synovial).

2.2. Case definitions

A case was enrolled as CAP (all-cause) if a hospitalized patient presented within 72 h of admission with a new or evolving pulmonary infiltrate on chest radiograph suggestive of pneumonia (as interpreted by the treating physician or radiologist), which was associated with two or more of the following signs or symptoms: temperature > 38 °C; cough; sputum production; shortness of breath; pleuritic chest pain; crackles, or consolidation upon chest examination. Patients were excluded if they failed to meet the CAP case definition, were discharged, refused consent, or were

from a long term care facility. CAP_{Spn} was defined as a CAP case with laboratory confirmation of *S. pneumoniae* using PCV13-specific urine antigen detection (UAD_{PCV13}), or isolation of *S. pneumoniae* from blood or sputum culture. Bacteremic CAP_{Spn} was defined by isolation of *S. pneumoniae* from blood culture, and non-bacteremic CAP_{Spn} by isolation of *S. pneumoniae* from sputum culture or by a positive UAD_{PCV13} in a patient who tested negative by blood culture. A case was enrolled as IPD (non-CAP) if *S. pneumoniae* was isolated from a normally sterile site (e.g. blood, cerebrospinal fluid, pleural fluid or synovial fluid) in a patient without CAP.

2.3. Ethics

This study was approved by the research ethics boards (REB) at each participating hospital. Eligible patients or their legally authorized representative provided written informed consent for participation in the study. In the event that the patient died or consent could not be sought, patient demographics and outcome data were retrospectively collected from medical records in accordance with local REB approval.

2.4. Data collection

Data was collected from medical records and through patient interview. Details of the presenting respiratory illness signs and symptoms, chest radiography findings, admitting diagnosis, patient demographics, underlying co-morbidities, and immunization and social histories were collected. In addition, markers of severity and disease outcome were collected, including requirement for mechanical ventilation, intensive care unit (ICU) admission, length of hospital stay, and 30-day mortality.

2.5. Specimen collection and laboratory testing

All specimens and *S. pneumoniae* isolates recovered from routine culture at each CIRN SOS site were stored at −80 °C and shipped in batches on dry ice to the CIRN SOS Network central laboratory (Halifax, NS). Two hundred microliters of a *S. pneumoniae* suspension (1.0 MacFarlane) in PCR-grade water was subjected to a Total Nucleic Acid Isolation kit (Roche, Laval, QC) on a MagNA Pure LC 2.0 instrument, followed by elution in 100 μl, and 5 μl of the eluate was used as template for all PCR reactions. Real-time PCR targeting *lytA* and *cpsA* was used to confirm the presence of *S. pneumoniae*, and a combination of conventional and real-time multiplex PCR reactions were performed for serotype deduction [26,27]. For isolates where PCR was insufficiently discriminatory, Quellung reaction was performed at the National Microbiology Laboratory (Winnipeg, MB) using commercial pool, group, type, and factor antisera (Statens Serum Institute Diagnostica, Copenhagen, Denmark)[28]. Urine was stabilized with 25 mM PIPES buffer, pH 6.8 (Boston BioProducts, Ashland, MA) prior to freezing and tested using a UAD_{PCV13} on a Luminex 2.0 instrument at Pfizer's Vaccines Research and Development Laboratory (Pearl River, NY) [24,29,30].

2.6. Statistical analysis

A Fisher's exact test was used to compare proportions between the two study periods. For trend analyses, a non-parametric permutation test was used. For patient demographics and outcomes, univariate and multivariate regression analyses were performed. T-test and ANOVA were used for comparing continuous variables, and Chi square was used to compare categorical variables. A P value ≤ 0.05 was considered statistically significant for all tests. Each were performed using Statistical Analysis Software (SAS) version 9.4 (SAS Institute, Cary NC).

3. Results

3.1. Number of CAP and IPD cases identified and proportion of CAP attributed to S. pneumoniae

In this study period (years 2014–2015), 73 cases of IPD (non-CAP) and 4034 cases of all-cause CAP were enrolled and compared to previous data generated from years 2010 to 2013 [1]. Of the newly identified 4034 CAP cases, 1187 (29.4%) had a sputum culture, 2295 (56.9%) had blood cultures, and 1653 (41.0%) were tested using UAD_{PCV13} (Table S1). Of the 76.0% (6687/8803) of CAP cases where any test for *S. pneumoniae* was performed, *S. pneumoniae* positivity declined from 15.9% (134/845) in 2011 to 8.8% (148/1688) in 2014 (Fisher exact: P < 0.0001; trend: P = 0.04), but then increased to 12.9% (148/1148) in 2015 (P = 0.0005) (Table 1). Similarly in the 1198 CAP cases who had all laboratory tests performed, *S. pneumoniae* positivity decreased from 22.1% (25/113) in 2011 to 10.2% (36/353) in 2014 (Fisher exact: P = 0.0011; trend: P < 0.0001), and increased to 14.3% (32/224) in 2015 (P < 0.0001) (Table S2). Similar data was noted for individual tests (data not shown).

Table 1
Proportion of vaccine-preventable pneumococcal CAP among hospitalized adults who received any laboratory tests for *S. pneumoniae*.

Variable	Proportion (%) for select year(s)							
	2011[1]	2012[1]	2013[1]	2014	2015	2010–2013[1]	2014–2015	P value[2]
Tested[3]/CAP cases	82.7 (845/1022)	84.3 (1138/1350)	77.7 (1754/2258)	71.4 (1688/2364)	68.7 (1148/1670)	80.8 (3851/4769)	70.3 (2836/4034)	<0.0001
S. pneumoniae positive	15.9 (134/845)	14.8 (168/1138)	13.1 (229/1754)	8.8 (148/1688)	12.9 (148/1148)	14.3 (549/3851)	10.1 (286/2836)	<0.0001
Serotypeable results	71.6 (96/134)	70.2 (118/168)	69.4 (159/229)	72.3 (107/148)	74.6 (103/138)	69.9 (384/549)	73.4 (210/286)	0.290
Proportion of CAP cases tested[2]								
NVT[3]	1.3 (11/845)	0.7 (8/1138)	1.2 (21/1754)	0.7 (12/1688)	1.0 (12/1148)	1.0 (40/3851)	0.8 (24/2836)	0.396
PPV23 (non-PCV13)[3]	1.8 (15/845)	1.8 (21/1138)	2.1 (37/1754)	1.1 (18/1688)	1.7 (19/1148)	1.9 (75/3851)	1.3 (37/2836)	0.057
PCV7[3]	1.1 (9/845)	0.4 (5/1138)	0.8 (14/1754)	0.5 (8/1688)	0.6 (7/1148)	0.8 (29/3851)	0.5 (15/2836)	0.138
PCV13[3]	8.3 (70/845)	7.8 (89/1138)	5.8 (101/1754)	4.6 (77/1688)	6.3 (72/1148)	7.0 (269/3851)	5.3 (149/2836)	0.005
PCV13 (age 50+)[3]	7.1 (49/686)	6.8 (67/987)	5.2 (79/1510)	3.6 (52/1451)	5.8 (58/1003)	6.1 (201/3282)	4.5 (110/2454)	0.008
PCV13 (age 65+)[3]	5.2 (25/482)	6.0 (44/728)	4.2 (45/1082)	2.7 (27/986)	4.0 (29/719)	4.9 (117/2367)	3.3 (56/1705)	0.012

[1] Previously published data from LeBlanc et al. [1].
[2] *P* values represent comparisons between pneumococcal CAP cases between the two study periods.
[3] Number of results/total CAP cases tested by at least one diagnostic test for *S. pneumoniae* (sputum culture, blood culture, or PCV13-specific urine antigen detection).
Abbreviations: not available (NA); non-vaccine type (NVT); 7-valent pneumococcal conjugate (PCV7), 13-valent pneumococcal conjugate (PCV13); pneumococcal polysaccharide vaccine (PPV23).

3.2. Proportions of vaccine-preventable CAP

The contribution of PCV13 serotypes mirrored *S. pneumoniae* positivity in CAP cases where any test for *S. pneumoniae* was performed (Table 1). A significant decline was noted between study periods (2010–2013 vs. 2014–2015; P = 0.0042), and over time, the proportion of PCV13 serotypes dropped from 8.3% (70/845) in 2011 to 4.6% (77/1688) in 2014 (Fisher exact P = 0.0002; trend: P = 0.04), but increased to 6.3% (72/1148) in 2015 (P = 0.047) (Table 1). Similar results were also seen for PCV13 serotypes in CAP cases where all diagnostic tests for *S. pneumoniae* were performed (Table S2), or when CAP_{Spn} cases were categorized by age (Table 1) or by disease categories (bacteremic or non-bacteremic CAP_{Spn}) (Table 2). Regardless of the categorization of CAP_{Spn} cases, no significant changes were noted for PCV7 serotypes, PPV23 (non-PCV13) serotypes, or non-vaccine types (NVTs) (Figs. S1–S5, Tables 1, S1, and S2).

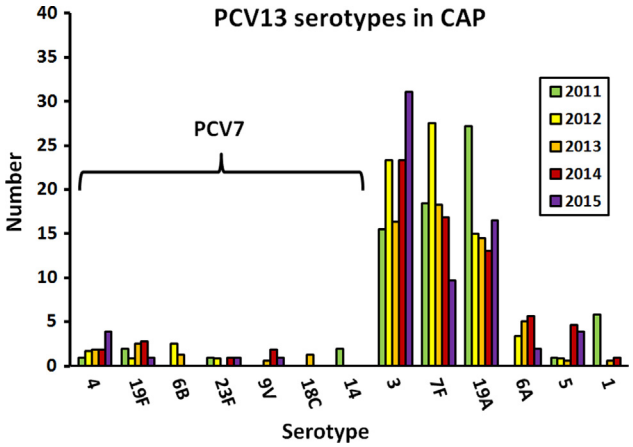

Fig. 1. *S. pneumoniae* serotype distribution by year in adults hospitalized with CAP for PCV7 and PCV13 serotypes.

3.3. S. pneumoniae serotype distribution over time

In CAP_{Spn} or IPD, PPV23 (non-PCV13) serotypes and NVTs remained relatively unchanged over time (Figs. S1, S2, S4 and S5; Tables 1, S1 and S2). In contrast, a decline in *S. pneumoniae* positivity and PCV13 serotypes over time was noted in CAP cases. This decline in PCV13 serotypes over time was attributed primarily to a reduction in serotype 7F, and to a rapid decline in serotype 19A after 2011 (Fig. 1). Of the serotypeable results, serotype 7F declined from 18.5% to 9.7% from 2011 to 2015 (P = 0.037). For serotype 19A, a decline of 27.2% to 16.5% was observed for the same time period (P = 0.032); however, unlike serotype 7F, there was an initial decline after 2011, and a plateau observed in subsequent years. Serotype 3, on the other hand, increased from 15.5% to 31.1% (P = 0.002). Compared to CAP, low numbers of IPD (non-CAP) cases were identified (Fig. S3), but these showed similar declines over time for serotype 7F, and variable results for serotypes 3 and 19A. With PCV13 having been shown to afford some protection against serotype 6C IPD through cross-reactive antibodies to serotype 6A [31,32], serotype 6C (a NVT) was also analyzed over time. In CAP_{Spn} cases, no serotype 6C cases were observed after 2013, but small numbers remained in IPD (non-CAP) (Figs. S2 and S5).

3.4. Patient demographics

The mean age of the 286 CAP_{Spn} cases identified between years 2014 and 2015 was 62.2 years, which was younger than *S. pneumoniae*-negative CAP cases at 68.8 years (P = 0.010), but not different from CAP_{Spn} cases from years 2010–2013 (P = 0.882) (Table 3). As previously observed for years 2010–2013 [1], the proportion of CAP_{Spn} in the 2014–2015 period increased with age, and most occurred in the ≥65 and ≥50 age cohorts (46.2% and 77.6%, respectively). The majority of CAP_{Spn} cases had underlying medical co-morbidities (P < 0.0001), but *S. pneumoniae*-negative CAP cases had a higher proportion of pulmonary, cardiac, vascular, or endocrine co-morbidities. No differences were noted in immunocompromising conditions or receipt of antibiotics between *S. pneumoniae*-positive and -negative cohorts, or between CAP_{Spn} cases for both study periods. Amongst patients in whom pneumococcal vaccine status was available, approximately half of patients had been vaccinated and the coverage rate did not differ between CAP_{Spn} cases between the two study periods (P = 0.548). In contrast, in *S. pneumoniae*-negative CAP cases, a significant increase (P < 0.0001) in vaccine coverage was noted (53.7% for 2010/2013 vs. 73.8% for 2014–2015). No significant differences were noted for vaccine brand over time, with 95% having received PPV23 in both *S. pneumoniae*-negative CAP and CAP_{Spn} cases. Overall, the patient demographics for cases of CAP and CAP_{Spn} were relatively unchanged over the study periods and were consistent with our previous study [1]. With the exception of mean age (62.3 in 2010–2013 vs. 66.0 2014–2015; P = 0.001) and the proportion of immunocompromised individuals (44.4% in 2010–2013 vs. 24.7% in 2014–2015; P = 0.010), no significant differences were noted in the IPD (non-CAP) cases over the two study periods (Table S3). It should be noted that the numbers were small for IPD (non-CAP) cases in both time periods (n = 81 and 73, respectively).

Table 2
Proportion of PCV13 serotypes in adults hospitalized with bacteremic or non-bacteremic pneumococcal CAP.

Variable	Proportion (%) for select year(s)							
	2011[1]	2012[1]	2013[1]	2014	2015	2010–2013[1]	2014–2015	P value[2]
Bacteremic CAP_{Spn}[3]	9.0 (65/726)	8.4 (76/902)	6.5 (90/1380)	5.1 (70/1370)	6.6 (61/925)	7.7 (239/3110)	5.7 (131/2295)	0.040
Non-bacteremic CAP_{Spn}[4]								
Total[4]	5.6 (30/535)	7.5 (60/803)	5.3 (69/1309)	2.3 (37/1624)	4.6 (51/1109)	5.9 (161/2708)	4.2 (88/2104)	0.008
BC negative[5]	6.0 (25/416)	8.2 (47/571)	6.2 (58/935)	2.3 (30/1306)	4.5 (40/886)	6.6 (131/1971)	4.5 (70/1563)	0.007
BC not performed[6]	4.2 (5/119)	5.6 (13/232)	2.9 (11/374)	2.2 (7/318)	4.9 (11/223)	4.1 (30/737)	3.3 (18/541)	0.458

[1] Previously published data from LeBlanc et al. [1].
[2] *P* values represent comparisons between pneumococcal CAP cases between the two study periods.
[3] Number of PCV13 serotypes per CAP cases tested by blood culture.
[4] Number of PCV13 serotypes per CAP that were tested by sputum and/or UAD_{PCV13}.
[5] Number of PCV13 serotypes per CAP cases that were tested by sputum and/or UAD_{PCV13}, and had negative blood cultures.
[6] Number of PCV13 serotypes per CAP cases tested by sputum and/or UAD_{PCV13}, but blood cultures were not performed. As blood cultures were not performed, a subset of these CAP_{Spn} included here could be misclassified as non-bacteremic CAP_{Spn}. Abbreviations: Blood culture (BC); not available (NA); 13-valent pneumococcal conjugate (PCV13).

Table 3
Demographics and clinical outcomes of hospitalized adults with CAP.

Variable	Results and time period				P value Spn-positive vs. negative for 2010/2013[3,4]	P value Spn-positive vs. negative for 2014/2015[5]	P value Spn-positive 2010/2013 vs. 2014/2015[6]
	Spn-negative[1]		Sp-positive[2]				
	2010–2013[3] (n = 3302)	2014–2015 (n = 2550)	2010–2013[3] (n = 549)	2014–2015 (n = 286)			
Demographics							
Age, mean (range)	68.5 (17–104)	68.8 (18–108)	62.4 (20–100)	62.2 (19–103)	0.012	0.010	0.882
Age 16–49 (%)	13.5 (447/3302)	12.5 (318/2550)	22.2 (122/549)	22.4 (64/286)	<0.0001	<0.0001	0.948
Age 65+ (%)	63.9 (2110/3302)	64.3 (1639/2550)	47.0 (258/549)	46.2 (132/286)	<0.0001	<0.0001	0.826
Age +50 (%)	86.5 (2885/3302)	87.5 (2232/2550)	77.8 (427/549)	77.6 (222/286)	<0.0001	<0.0001	0.948
Gender (male) (%)	53.7 (1772/3302)	54.3 (1385/2550)	53.9 (296/549)	50.4 (144/286)	0.931	0.210	0.337
$\geq$ 1 co-morbidity (%)	93.8 (3098/3302)	94.0 (2397/2550)	88.2 (484/549)	86.7 (248/286)	<0.0001	<0.0001	0.532
Immunocompromised (%)	31.2 (1030/3302)	24.8 (631/2550)	27.9 (153/549)	23.4 (67/286)	0.121	0.603	0.162
Current/past smoker (%)[7]	68.0 (2096/3081)	69.7 (1628/2337)	70.6 (370/524)	72.5 (190/262)	0.237	0.349	0.597
Obesity, body mass index $\geq$ 30 (%)[7]	25.8 (734/2841)	29.3 (641/1909)	21.3 (102/479)	25.5 (63/247)	0.053	0.215	0.201
Concomitant influenza infection; (%)[7]	13.9 (220/1588)	21.9 (461/2109)	15.6 (43/276)	20.2 (48/238)	0.455	0.547	0.174
Pneumococcal vaccine (%)[7]	53.7 (1200/2235)	73.8 (1101/1492)	53.8 (163/303)	56.8 (84/148)	0.974	<0.0001	0.548
Pneumococcal vaccine brand documented (%)[8]	63.1 (757/1200)	65.3 (719/1101)	61.3 (100/163)	65.5 (55/84)	0.656	0.970	0.519
PCV10 (%)[9]	1.2 (9/757)	0.8 (6/719)	3.0 (3/100)	0.0 (0/55)	0.152	0.511	0.198
PCV13 (%)[9]	1.6 (12/757)	4.0 (29/719)	2.0 (2/100)	5.5 (3/55)	0.768	0.589	0.241
PPV23 (%)[9]	97.2 (736/757)	95.1 (684/719)	95.0 (95/100)	94.5 (52/55)	0.230	0.843	0.893
Time to first antibiotic $\leq$ 4hrs (%)[7]	68.3 (2073/3033)	71.1 (1707/2402)	72.6 (371/511)	75.6 (207/274)	0.052	0.118	0.363
Time to first antibiotic $\leq$ 8hrs (%)[7]	86.3 (2618/3033)	88.3 (2120/2402)	88.3 (451/511)	88.0 (241/274)	0.220	0.884	0.901
Clinical outcomes							
30-day mortality (%)	11.4 (375/3302)	11.5 (292/2550)	9.7 (53/549)	5.9 (17/286)	0.242	0.004	0.086
LOS in days [mean (range; Q75)]	11.8 (1–384; 14)	10.8 (1–136; 13)	12.5 (1–105; 14)	9.9 (1–126; 11)	0.238	0.546	0.005
ICU admission (%)	17.7 (584/3302)	18.3 (467/2550)	29.3 (161/549)	30.4 (87/286)	<0.0001	<0.0001	0.741
Mechanical ventilation (%)	11.7 (386/3302)	11.3 (289/2550)	20.2 (111/549)	20.3 (58/286)	<0.0001	<0.0001	0.973
Any complication (%)	53.6 (1769/3299)	54.1 (1376/2550)	57.1 (313/549)	53.5 (153/286)	0.128	0.847	0.320

[1] CAP cases testing negative by sputum culture, blood culture, or UAD_{PCV13}.
[2] CAP with positive result from UAD_{PCV13} or *S. pneumoniae* (Spn) culture from blood or sputum.
[3] Previously published data from LeBlanc et al. [1].
[4] *P* values represent comparisons between pneumococcal and non-pneumococcal CAP cases between years 2010–2013.
[5] *P* values represent comparisons between pneumococcal and non-pneumococcal CAP cases between years 2014–2015.
[6] *P* values represent comparisons between pneumococcal CAP cases between the two study periods.
[7] Denominators reflect numbers of cases where data was available.
[8] Denominators represents cases having received pneumococcal vaccine whereas numerators are the number where vaccine brand was documented.
[9] Denominators represents individuals where the vaccine brand was documented whereas numerators are the proportion of each vaccine.

3.5. Clinical outcomes

As previously reported [1] for years 2010–2013, clinical outcomes such as admission to ICU and requirement for mechanical ventilation were more prominent in CAP_{Spn} compared to *S. pneumoniae*-negative CAP cases in years 2014–2015 ($P < 0.0001$) (Table 3). Unlike study period 2010–2013, significant lower mortality was observed when comparing CAP_{Spn} cases to all-cause CAP cases in years 2014–2015 ($P = 0.004$). When comparing CAP_{Spn} cases between study periods, mortality nearly achieved significance ($P = 0.086$). In a univariate analysis, there was also a significant decrease ($P = 0.005$) in mean length of hospital stay for CAP_{Spn} cases in 2014–2015 compared to those from years 2010–2013, but no differences were noted when comparing CAP_{Spn} cases from either study period to *S. pneumoniae*-negative CAP cases. Admission to the ICU and requirement for mechanical ventilation remained unchanged in CAP_{Spn} cases when comparing both study periods ($P = 0.741$ and $P = 0.973$, respectively), but both were significantly more frequent than in *S. pneumoniae*-negative CAP cases ($P < 0.0001$), as previously described [1]. Over 50% of all *S. pneumoniae*-positive and negative CAP cases experienced complications, but no significant differences were noted between groups or study periods. Multivariate did not reveal any significant differences in clinical outcomes for CAP_{Spn} cases over time.

4. Discussion

It is well recognized that both PCV7 and PCV13 have had a significant impact on pneumococcal disease epidemiology, through both direct and indirect effects (i.e. herd immunity). With the anticipated herd immunity conferred by PCV13 childhood immunization introduced in all Canadian provinces by January 2011, this study compared previously published data from CIRN SOS Network from years 2010–2013 [1] to more recent years (2014–2015), and analyzed trends over all study years. Overall, no significant changes were noted for patient demographics or serious clinical outcomes for CAP cases, but the proportion of CAP_{Spn} cases and *S. pneumoniae* serotype distribution varied significantly over time. Our data suggests that herd immunity afforded to adults through childhood immunization with PCV13 was evident for serotypes 7F and 19A, but this response was accompanied by a concomitant proportional increase in serotype 3. Similar trends were seen when data was categorized by age groups, by laboratory tests (any or all test performed), or by disease categories (bacteremic or non-bacteremic CAP_{Spn}).

IPD cases outside of bacteremic CAP [i.e IPD (non-CAP)] were analysed separately, and showed the same trends over time for serotypes 3, 7F, and 19A (Fig. S3). It should be noted that when comparing the 2010–2013 and 2014–2015 time periods (Table S3), significant differences were noted in IPD(non-CAP) patient demographics in terms of age and immunocompromize, but little conclusions could be drawn from these findings given the small numbers for each. This data is consistent with others who have reported that pneumococcal disease in adults predominantly manifests as pneumonia with or without bacteremia, unlike the predominance of IPD (i.e. meningitis) seen in young children [11]. Therefore, this study focussed its analyses on adults hospitalized with pneumococcal CAP, and divided these into bacteremic (i.e CAP and IPD) and non-bacteremic pneumococcal CAP (i.e. CAP only).

The bacteremic CAP_{Spn} data from this study is in part consistent with those obtained in Canadian national IPD surveillance which showed a progressive decline in PCV13 serotype 7F [18]. However, in contrast to the progressive decline of serotype 19A seen in national IPD surveillance, our study showed an initial decline, followed by a plateau after 2011 among patients hospitalized with bacteremic CAP_{Spn} [18]. National IPD surveillance showed stable rates of serotype 3 from years 2012 to 2016 [18], whereas our data showed a significant relative increase in the proportion of serotype 3 over time. IPD surveillance in other countries have also noted a decline in serotype 7F over time, and variable responses for serotypes 19A and 3 [6,33–48]. In the current study, the timing of herd immunity in bacteremic CAP_{Spn} is consistent with IPD surveillance studies [18,33], and appeared as early as the second year following introduction of PCV13 in childhood immunization for serotype 19A, or a year later for serotype 7F [8]. To date, it is unclear whether maximal impact of herd immunity has been reached.

Non-bacteremic CAP_{Spn} cases demonstrated similar trends over time for PCV13 serotypes, but these cases are likely underestimated in all study years. While non-bacteremic CAP_{Spn} is increasingly being recognized as an important contributor to morbidity and mortality [1,4,40,45,45], the collection of urine for pneumococcal antigen detection is not common practice in clinical laboratories. Depending on the study period, only a third of CAP patients had a sputum culture (29.4–34.3%), and of theses, only 44–47% of *S. pneumoniae* isolates from sputum were archived for subsequent serotyping analyses (Table S1). In comparison, 57–65% of patients had blood cultures, with 74–78% available for serotyping (and national IPD surveillance) (Table S1). The benefits of sputum culture and UAD_{PCV13} in the identification of non-bacteremic CAP_{Spn} have been documented [1,33,40,45]. A recent study demonstrated a reduction in PCV13 serotypes in adults using blood culture and a UAD_{PCV13}, but their analyses did not discriminate cases of bacteremic and non-bacteremic CAP_{Spn} [33]. To our knowledge, this study is the first study to demonstrate herd immunity from PCV13 childhood immunization in adults hospitalized with non-bacteremic CAP_{Spn}.

Whether in bacteremic or non-bacteremic CAP_{Spn}, serotype 3 increased in proportion over time despite herd immunity observed with serotypes 7F and 19A. However, it should be noted that the proportional increase in serotype 3 may simply be a reflection persistence, with a concomitant proportional decrease serotypes 7F and 19A. The persistence of serotype 3 is congruent with recent IPD surveillance studies [18,21,36,47], but the reason remains unclear. In some studies, PCV13 was not effective in reducing serotype 3 colonization in children [48], and as such, may be insufficient to provide protection to adults through herd immunity [41–46]. In a recent commentary by Dr. DeWals [47], several possible explanations for the persistence of serotype 3 were discussed. These included differences in capsule biosynthesis, virus-specific virulence factors like invasiveness, and host-related factors like immunotolerance. Poor serotype 3 vaccine effectiveness with the current vaccine schedules and doses may also be contributing [47]. While it remains to be seen if serotype 3 will decline in subsequent years through herd immunity, better protection may be afforded through direct adult immunization.

In healthy adults aged $\geq$65 years, the CAPiTA trial demonstrated that direct immunization with PCV13 was effective against all PCV13 serotypes [24]. Data from this study and our previous publication [1] showed that most CAP_{Spn} cases (78%) occurred in patients aged $\geq$50, whereas only 47% were in adults aged $\geq$65. This data suggests that consideration of expansion of vaccine recommendations to include the 50–65 year old age cohort may have value, as recognized in other countries [25]. After the recent interim recommendations in Canada for PCV13 use in adults $\geq$65 years [8,9], it remains to be seen whether direct immunization will achieve better protection of adults against PCV13 serotypes, particularly serotype 3, or whether new vaccine formulations or a revision of vaccine schedules will be required.

The strengths of this study include active surveillance for CAP and IPD in hospitalized adults, confirmation of CAP with diagnostic imaging and compatible signs and symptoms, and the various lab-

oratory methods used to increase detection of *S. pneumoniae*. Traditionally, pneumococcal disease surveillance in Canada relied solely on IPD isolates, which are submitted to reference laboratories voluntarily. With the smaller incidence of IPD compared to CAP in adults [11], small changes in serotype distribution could be difficult to differentiate from random secular trends [39]. While this study was not designed to capture the true incidence of CAP, active surveillance by the CIRN SOS Network has the advantage of generating geographically representative data across Canada, and data on vaccine-preventable *S. pneumoniae* presented over time as proportional contributions of denominators like overall cases of CAP. The main limitations of this study are consistent with other studies [1,33]. Some CAP cases were not captured due to lack of consent, refusal, or failure to meet case definitions, and some data for patient demographics was not available like immunization status and vaccine brand. Not all laboratory tests were performed on every CAP case, and only serotypeable results contributed to the serotype distribution. Finally, the significant increase ($P < 0.0001$) in PPV23 use in the *S. pneumoniae*-negative CAP group in years 2014–2015 makes it difficult to completely exclude direct effects of this vaccine against CAP caused by serotypes common to PPV23 and PCV13, as opposed to herd immunity from PCV13-based childhood immunization. The role of PPV23 in preventing CAP_{Spn} has been subject to much debate given the heterogeneity in study case definitions, diversity in patient populations tested, coverage in pediatric vaccine programs, changes pneumococcal serotype epidemiology, methodology used to identify CAP_{Spn} and timing of vaccination and testing [49–52]. Given recent *meta*-analyses [49–52] on use of PPV23 in adults which failed to demonstrate effectiveness of PPV23 for the prevention of CAP, it is doubtful that the observed reduction in CAP_{Spn} in the current study can be attributed to increased use of PPV23 [49–52].

In the current study, the proportion of PPV23 serotypes (as well as NVTs) were likely underrepresented by using UAD_{PCV13} [1]. Given this limitation, the use of proportions has to be interpreted with caution. If significant changes would arise in CAP_{Spn} cases caused by PPV23(non-PCV13) serotypes or NVTs, this could skew the proportional contributions to CAP of PCV13 serotypes. However, no decline over time was observed for PPV23(non-PCV13) serotypes. Data from blood or sputum did not show any significant changes over time for PPV23(non-PCV13) or NVTs (Table S1 and Figs. S1 and S2), and trends over time for CAP_{Spn} caused by PCV13 serotypes were similar for each method used (Table S1), and for bacteremic or non-bacteremic CAP_{Spn} (Table 2). This data suggests that UAD_{PCV13} aids in the detection of CAP_{Spn} caused by PCV13 serotypes, but is not solely driving the changes in PCV13 serotypes over time. On the other hand, the proportional contributions to non-bacteremic CAP_{Spn} of PPV23(non-PCV13) serotypes and NVTs would be better described if UAD methods able to detect these serotypes were available. Such methods have yet to be developed. To further our understanding of the contributions of UAD_{PCV13} to the overall proportion of PCV13 results, methodological studies are underway comparing UAD_{PCV13} results to those obtained using blood and sputum culture, as well as a commercial pan-pneumococcal urine antigen assay. The later was not included in this study as it did not provide serotype data.

Regardless of this study's limitations, the methodologies used in this study have remained unchanged over the study years, which allowed for relative comparisons and trend analyses over time. The robustness of our conclusions are supported by the fact that all data displayed similar trends; regardless of testing methodology, age (all adults ≥16, the ≥65 cohort, or those ≥50 years), or whether CAP_{Spn} patients were categorized by disease categories (bacteremic and non-bacteremic CAP_{Spn}).

Overall, this study demonstrated that herd immunity from childhood immunization was observed in adults hospitalized with CAP_{Spn}, and this was mostly attributed to declines in serotypes 7F and 19A. Despite these successes, serotype 3 persisted in recent years, and the residual burden of CAP_{Spn} and IPD cases was evident. PCV13 serotypes accounted for an estimated 5–8% of hospitalized CAP in most recent years, compared to 10–18% three years prior. For now, our data supports the recent interim recommendation by NACI for the use of PCV13 in adults aged ≥65 years [8], but it is unclear whether herd immunity is complete. Ongoing surveillance will be required, and it will be interesting to evaluate whether serotype 3 will decline in subsequent years if PCV13 becomes more widely used in Canadian adults.

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Author contributions

The CIRN SOS principal investigator (SAM) and CIRN SOS site investigators (AEM, AM, DW, GB, JJ, JL, KG, LV, MA, ML, MS, ST, WB) were involved in the conception and design of the study; SAM, JL, TH, and ME conducted/supervised the CIRN SOS Network central laboratory; SAM, ME, and AA were involved in CIRN SOS site coordination. DM-C, LY, and JL were involved in data management and statistical support. JL, AL, HG, WD, and IM were involved in method development and molecular testing for the study. IM provided reference serological testing at the NML. JL drafted the manuscript and interpreted the data. All authors revised the manuscript and provided important intellectual content, and agree with the final version submitted for publication.

Declaration of Competing Interest

SAM received research grants from GlaxoSmithKline, Pfizer, Sanofi Pasteur; LV received research grants from GlaxoSmithKline, Pfizer, Optimer, Cubist and Merck, and personal fees from Merck, Optimer and Cubist. No other conflicts were declared.

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Appendix A. Supplementary material

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