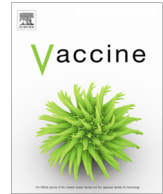




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Population-based incidence of invasive pneumococcal disease in children and adults in Ontario and British Columbia, 2002–2018: A Canadian Immunization Research Network (CIRN) study



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ABSTRACT

Background: Invasive pneumococcal disease (IPD) burden, evaluated in Canada using reported confirmed cases in surveillance systems, is likely underestimated due to underreporting. We estimated the burden of IPD in Ontario and British Columbia (BC) by combining surveillance data with health administrative databases.

Methods: We established a cohort of 27,525 individuals in Ontario and BC. Laboratory-confirmed IPD cases were identified from Ontario's integrated Public Health Information System and the BC Centre for Disease Control Public Health Laboratory. Possible IPD cases were identified from hospitalization data in both provinces, and from emergency department visit data in Ontario. We estimated the age and sex adjusted annual incidence of IPD and pneumococcal conjugate/polysaccharide vaccine (PCV/PPV) serotype-specific IPD using Poisson regression models.

Results: In Ontario, 20,205 overall IPD cases, including 15,299 laboratory-confirmed cases, were identified with relatively stable age- and sex-adjusted annual incidence rates ranging from 13.7/100,000 (2005) to 13.6/100,000 (2018). In BC, 7,320 overall IPD cases, including 5,932 laboratory-confirmed cases were identified; annual incidence rates increased from 10.9/100,000 (2002) to 13.2/100,000 (2018). Older adults aged ≥ 85 years had the highest incidence rates. During 2007–2018 the incidence of PCV7

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serotypes and additional PCV13 serotypes decreased while the incidence of unique PPV23 and non-vaccine serotypes increased in both provinces.

Conclusions: IPD continues to cause a substantial public health burden in Canada despite publicly funded pneumococcal vaccination programs, resulting in part from an increase in unique PPV23 and non-vaccine serotypes.

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1. Introduction

Streptococcus pneumoniae causes substantial medical and economic burden through a broad spectrum of manifestations, including invasive pneumococcal disease (IPD) and non-invasive disease such as community-acquired pneumonia (CAP) and acute otitis media (AOM) [1,2]. IPD is the “more severe and invasive pneumococcal infections, such as bacteraemia, sepsis, meningitis and osteomyelitis, in which the bacterium can be isolated from normally sterile sites” [3], and is a readily enumerated pneumococcal disease [4,5] because laboratory-confirmed IPD (‘confirmed IPD’ hereafter) cases are reportable in many countries. The national incidence of confirmed IPD in Canada was 9.5 per 100,000 in 2017 [6]. However, using confirmed IPD cases alone underestimates true IPD burden [7–10] for many reasons including underreporting [11], relatively low rates of bacteremia detection after antibiotic therapy before sample collection, and intermittent bloodstream invasion by *S. pneumoniae* [12]. Of note, antimicrobial stewardship programs have been in place in acute care hospitals in Canada since 2013 [13]. British Columbia and Alberta initiated the community program “Do bugs need drugs?” to reduce inappropriate antibiotic prescribing; some components of the program are also used in other jurisdictions [14,15]. The national campaign “Using Antibiotics Wisely” was developed in 2017 to reduce inappropriate antibiotic use in community care settings, primarily for respiratory tract infection in primary care and urinary tract infection in long-term care [16].

There are limited data on the comprehensive burden of IPD both across the lifespan and during different childhood pneumococcal conjugate vaccine (PCV) program periods in Canada. In 2002, the 7-valent PCV7 vaccine was recommended for routine infant immunization in Canada [17]. In 2010, the National Advisory Committee on Immunization (NACI) suggested replacing PCV7 with PCV13 and switching from the 4-dose schedule to a 3-dose schedule [18]. Most provinces switched to PCV13 during 2010–2011. Few provinces, including Ontario used PCV10 from October 2009 to October 2010, and then transitioned to PCV13. Quebec switched back to PCV10 in May 2018 following the recommendation from a provincial expert committee, and currently has a mixed schedule of two doses of PCV10 and one dose of PCV13 [19]. Publicly funded 23-valent pneumococcal polysaccharide vaccine (PPV23) has been available for adults aged 65 years and older and high-risk individuals following the NACI recommendation in 1989.

We conducted a population-based retrospective study in two Canadian provinces, Ontario (population: 15 million) and BC (population: 5 million), which account for about 53% of the Canadian population [20], to estimate the annual incidence and age group-specific incidence by PCV periods in children and adults over a 17-year period. Our secondary aim was to determine whether the trends in IPD incidence differed between confirmed IPD cases and trends when we also included possible cases from health administrative databases over time and across PCV periods.

2. Materials and methods

2.1. Data sources

We established a cohort of 27,525 individuals in Ontario and BC. We used population-based laboratory and health administrative databases to identify IPD cases from 2005 to 2018 in Ontario and 2002–2018 in BC. Confirmed IPD cases were identified from Ontario’s integrated Public Health Information System (iPHIS) and the BC Centre for Disease Control (BCCDC) Public Health Laboratory data (PHL) [9,21]. Possible cases without laboratory confirmation (‘possible IPD’ hereafter) are not reportable but can be identified from administrative databases [11]. Possible IPD cases included hospitalizations identified from the Discharge Abstract Database (DAD) in Ontario and BC [22], and emergency department (ED) visits identified from the National Ambulatory Care Reporting System (NACRS) in Ontario using diagnostic codes from the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada* (ICD-10-CA) [23]. ED visit data were not available for BC. Information on age and sex were obtained from the Registered Persons Database in Ontario and the Medical Services Plan Registration and Premium Billing patient registry in BC [24,25]. Data were analyzed separately in Ontario and BC using similar methods. The Ontario datasets were linked using unique identifiers and analyzed at ICES. BC datasets were also linked using unique identifiers and analyzed at Population Data BC.

2.2. Outcomes/definitions

A confirmed IPD case was defined as isolation of *Streptococcus pneumoniae* and/or identification of *S. pneumoniae* DNA from a normally sterile site (e.g., blood, cerebrospinal fluid, synovial or peritoneal fluid, bone, excluding middle ear) reported in iPHIS and BCCDC PHL data [26]. Confirmed IPD cases with information on serotype were grouped into four categories: 1. cases with any of the serotypes covered by PCV7 (4, 6B, 9V, 14, 18C, 19F and 23F) as ‘PCV7’, 2. cases with any of the six serotypes in PCV13 but not in PCV7 (1, 3, 5, 6A, 7F, 19A) as ‘additional PCV13’, 3. cases with any of the 11 serotypes uniquely covered by PPV23 (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F and 33F) as ‘unique PPV23’, and 4. cases with non-vaccine serotypes (serotypes that are not included in any formulation) as ‘non-vaccine’. We linked possible IPD cases in each administrative database with the confirmed IPD cases. Possible IPD was defined as case hospitalized (DAD) or seeking emergency care (NACRS) with an assigned primary or secondary ICD-10-CA code for the following conditions (irrespective of laboratory confirmation) [23]: pneumococcal meningitis (ICD-10-CA: G00.1), pneumococcal septicemia (ICD-10-CA: A40.3), pneumococcus elsewhere (e.g., infective pericarditis, acute peritonitis, puerperal sepsis, and congenital pneumonia) (ICD-10-CA: B95.3), or pneumococcal arthritis and polyarthritis (ICD-10-CA: M00.1) [27]. We combined confirmed IPD cases with the possible IPD cases and considered them as ‘Overall IPD’. We presented results separately for ‘overall IPD’ and ‘confirmed IPD’ as our two outcomes.

Duplicate records within a database were identified and excluded using unique identifiers and the following dates in each database: episode date in iPHIS, collection date in BC CDC PHL data, admission date in DAD, and registration date in NACRS. Along with the unique identifiers, the following dates were used as index dates for the outcomes to link databases, and to identify duplicate records and recurrent episodes across databases: episode date (iPHIS), collection date (BC CDC PHL data), discharge date (DAD) to account for the length of hospital stay when a patient has not recovered and not susceptible for reinfection, and registration date (NACRS). IPD records across databases within 30 days of the earliest index date were considered duplicates; the earliest index date was retained. IPD episodes within 30 days of the earliest index date were considered same episodes; IPD episodes > 30 days of the earliest index date were considered recurrent episodes and included.

2.3. Statistical analyses

The study period was divided into three intervals in each province according to the childhood PCV immunization program periods: (1) PCV7 period, (2) PCV10 period, and (3) PCV13 period in Ontario, and (1) Pre-PCV baseline period, (2) PCV7 period, and (3) PCV13 period in BC (Table 1). Age was categorized into the following groups: 0–4 years, 5–17 years, 18–39 years, 40–64 years, 65–74 years, 75–84 years and ≥85 years. We estimated incidence rates for overall IPD, confirmed IPD, and serotype-specific IPD. We excluded cases with unreported, or missing serotype and subtype for calculating serotype-specific incidence rates. Poisson regression models were fitted to estimate annual crude incidence rate, and annual incidence rates (95% confidence intervals [CIs]) adjusted for age group and sex of the IPD cases using annual population estimates from Statistics Canada as the offset parameter [28]. We also estimated age group-specific incidence rates of overall and confirmed IPD according to the PCV vaccine program periods in the provinces. Serotype-specific incidence rates (annual and age group-specific) were calculated from 2007 to 2018 for both provinces because routine reporting of serotype for confirmed IPD started in 2007 in Ontario. All analyses were conducted using SAS 9.4 (SAS Institute) software.

2.4. Ethics approval

We obtained ethics approval from the Ethics Review Boards of the Ontario Agency for Health Protection and Promotion, the University of British Columbia and BC Ministry of Health.

Table 1
Three study intervals according to the pneumococcal conjugate vaccine (PCV) immunization program periods and dose schedule in Ontario and British Columbia, 2002–2018.

PCV period	Calendar time	Dose schedule
Ontario		
PCV7	1 January 2005 to 30 September 2009	4-dose: 2, 4, 6, and 15 months
PCV10	1 October 2009 to 31 October 2010	4-dose: 2, 4, 6, and 15 months
PCV13	1 November 2010 to 31 December 2018	3-dose: 2, 4, and 12 months
British Columbia		
Pre-PCV baseline period	1 January 2002 to 31 August 2003	–
PCV7	1 September 2003 to 31 May 2010	4-dose: 2, 4, 6, and 12–15 months
PCV13	1 June 2010 to 31 December 2018	3-dose: 2, 4, and 12 months

Abbreviations: PCV7, PCV10, and PCV13, the 7-valent, 10-valent, and 13-valent pneumococcal conjugate vaccine, respectively.

3. Results

In Ontario, 20,205 overall IPD cases, of which 15,299 were confirmed IPD, were identified during 2005–2018. In BC, 7,320 overall IPD cases, including 5,932 confirmed IPD, were identified during 2002–2018. However, 48% and 54% of confirmed IPD in Ontario and BC, respectively, could not be linked to the possible IPD cases in the administrative databases. Possible IPD cases contributed an additional 24% cases (17% from hospitalization and 7% from ED visits) in Ontario and 19% cases (from hospitalization) in BC. Among all IPD cases with information available on sex and age, more than half of the cases were in males in both provinces (Table 2). Of the confirmed IPD cases with known age and sex identified during 2007–2018, 79.3% (10,682/13,473) of cases in Ontario and 99% (4,425/4,480) of cases in BC had information on serotype (Table 2). Serotype was not reported in 2,759 (20.5%) of IPD cases and was ungroupable in 32 (0.2%) of IPD cases in Ontario, while serotype was not reported in 11 (0.3%) of IPD cases and was ungroupable in 44 (1%) of IPD cases in BC.

3.1. Annual incidence trends

Ontario had relatively stable crude annual incidence rates of overall IPD ranging from 10.2/100,000 (2005) to 11.2/100,000 (2018) with higher rates during 2009–2012 (Fig. 1A, Supplementary Table 1). In BC, the crude incidence rate increased from 9.1/100,000 in 2002 to 14.0/100,000 in 2007 and then decreased to 6.9/100,000 in 2010 before gradually increasing again to 11.2/100,000 in 2018 (Fig. 1B, Supplementary Table 1). After adjustment for age and sex, incidence rates increased in both provinces. Confirmed IPD cases followed the same trend over time as overall IPD cases but had a lower adjusted incidence rate, with a mean of 10.1 (95% CI: 9.9, 10.3) in Ontario and 9.2 (95% CI: 8.7, 9.7) in BC.

During 2007–2018 in Ontario, the age and sex adjusted incidence rate of PCV7 serotypes gradually decreased, while the incidence rate of unique PPV23 serotypes and non-vaccine serotypes increased (Fig. 1C, Supplementary Table 2); the incidence rate of additional PCV13 serotypes increased from 1.7/100,000 in 2007 to 4.8/100,000 in 2010 before decreasing to 2.0/100,000 in 2018. In BC, the age and sex adjusted incidence rate of PCV7 decreased from 1.9/100,000 in 2007 to 0.3/100,000 in 2013 before increasing again to 1.9/100,000 in 2018 (Fig. 1D, Supplementary Table 2); the incidence rate of additional PCV13 decreased from 6.0/100,000 in 2007 to 2.5/100,000 in 2018. The incidence rate of unique PPV23 serotypes increased from 2.6/100,000 to 3.9/100,000 and the incidence rate of non-vaccine serotypes increased from 1.5/100,000 in 2007 to 2.4/100,000 in 2018.

3.2. Age group-specific incidence according to PCV program period

In both Ontario and BC, the highest incidence rate of both overall and confirmed IPD was in older adults aged ≥ 85 years across all PCV program periods (Table 3, Table 4, Fig. 2A–2B). The lowest incidence rate was in the age group 5–39 years, while the incidence rate in children aged 0–4 years was higher than older children and adults aged 18–64 years but lower than older adults aged ≥ 65 years. In BC, prior to introduction of PCV7, children aged 0–4 years had the highest overall and confirmed IPD incidence rates, which declined sharply during the PCV7 period and further declined during the PCV13 period (Table 4, Fig. 2B). The trends in age-specific incidence rate were similar for both overall and confirmed IPD cases. As expected, the rates were higher for overall IPD than for confirmed IPD in all age groups.

Table 2
Age and sex distribution of linked invasive pneumococcal disease cases in Ontario and British Columbia, 2002–2018.

Characteristics	Overall and confirmed IPD (2002–2018)		Confirmed IPD (2007–2018)			
	Overall IPD, n (%)	Confirmed IPD, n (%)	PCV7 serotype, n (%)	Additional PCV13 serotype, n (%)	Unique PPV23 serotype, n (%)	Non-vaccine serotypes, n (%)
Ontario	N = 20,197	N = 15,291	N = 973	N = 3,660	N = 3,210	N = 2,839
Sex						
Female	9,239 (46)	7,060 (46)	447 (45.9)	1,727 (47.2)	1,402 (43.7)	1,344 (47.3)
Male	10,958 (54)	8,231 (54)	526 (54.1)	1,933 (52.8)	1,808 (56.3)	1,495 (52.7)
Age group						
0–4 years	1,733 (9)	1,222 (8)	33 (3.4)	358 (9.8)	202 (6.3)	247 (8.7)
5–17 years	902 (4)	570 (4)	38 (3.9)	166 (4.5)	101 (3.1)	87 (3.1)
18–39 years	1,849 (9)	1,357 (9)	106 (10.9)	346 (9.5)	273 (8.5)	177 (6.2)
40–64 years	7,147 (35)	5,567 (36)	425 (43.7)	1,398 (38.2)	1,266 (39.4)	868 (30.6)
65–74 years	3,511 (17)	2,669 (17)	160 (16.4)	595 (16.3)	576 (17.9)	552 (19.4)
75–84 years	2,969 (15)	2,244 (15)	112 (11.5)	468 (12.8)	454 (14.1)	511 (18)
≥85 years	2,086 (10)	1,662 (11)	99 (10.2)	329 (9)	338 (10.5)	397 (14)
British Columbia	N = 7,117	N = 5,731	N = 611	N = 1,506	N = 1,359	N = 949
Sex						
Female	3,089 (43)	2,477 (43)	220 (36)	692 (46)	580 (43)	407 (43)
Male	4,028 (57)	3,254 (57)	391 (64)	814 (54)	779 (57)	542 (57)
Age group						
0–4 years	565 (8)	447 (8)	18 (3)	77 (5)	60 (4)	64 (7)
5–17 years	355 (5)	294 (5)	31 (5)	88 (6)	37 (3)	58 (6)
18–39 years	938 (13)	794 (14)	126 (21)	254 (17)	168 (12)	64 (7)
40–64 years	2,876 (40)	2,320 (40)	281 (46)	655 (43)	581 (43)	321 (34)
65–74 years	1,028 (14)	817 (14)	79 (13)	206 (14)	233 (17)	168 (18)
75–84 years	814 (11)	625 (11)	48 (8)	132 (9)	178 (13)	142 (15)
≥85 years	541 (8)	434 (8)	28 (5)	94 (6)	102 (8)	132 (14)

Abbreviations: IPD, invasive pneumococcal disease; PCV7, PCV10, and PCV13, the 7-valent, 10-valent, and 13-valent pneumococcal conjugate vaccine, respectively.

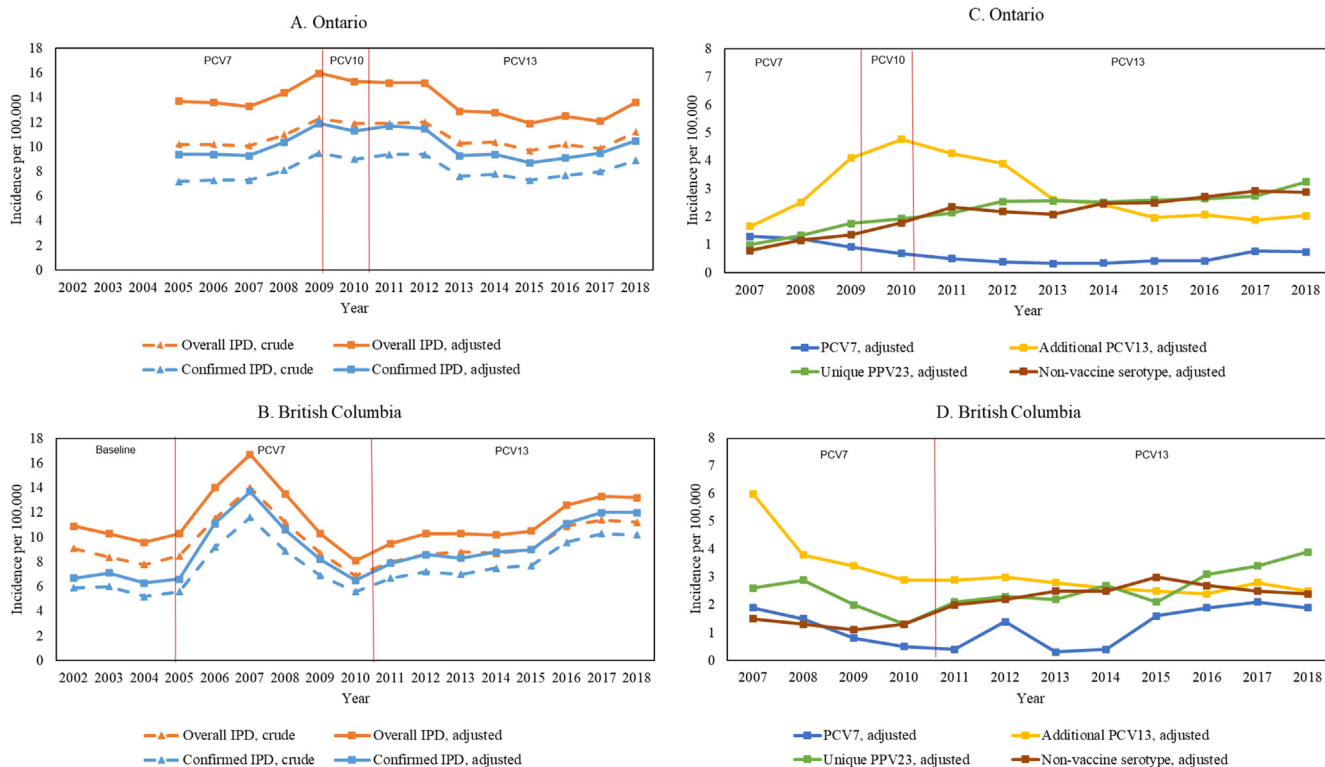


Fig. 1. Annual incidence of invasive pneumococcal disease (IPD): (A) Overall and confirmed IPD in Ontario (B) Overall and confirmed IPD in British Columbia (C) Serotype-specific IPD in Ontario (D) Serotype-specific IPD in British Columbia. Adjusted rates are adjusted for age group and sex.

In both Ontario and BC, older adults aged ≥ 85 years had the highest incidence rate of PCV7, additional PCV13, unique PPV23 and non-vaccine serotypes across all PCV program periods (Fig. 2C, Fig. 2C, Supplementary Table 3, Supplementary Table 4). The incidence rate of non-vaccine serotypes increased in older

adults aged ≥ 65 years during successive higher-valent PCV program periods in Ontario. In contrast, the incidence rate of additional PCV13, unique PPV23 and non-vaccine serotypes in BC were higher in older adults aged ≥ 65 years during PCV13 period than PCV7 period. Among children aged 0–4 years in Ontario, addi-

Table 3
Incidence of invasive pneumococcal disease according to age-group and pneumococcal conjugate vaccine (PCV) program periods in Ontario, 2005–2018.

Age group	Incidence per 100,000 population (95% Confidence interval)					
	PCV7 period		PCV10 period		PCV13 period	
	Overall IPD	Confirmed IPD	Overall IPD	Confirmed IPD	Overall IPD	Confirmed IPD
0–4 years	20.9 (19.0, 22.9)	13.9 (12.4, 15.6)	23.5 (16.1, 34.3)	16.8 (10.2, 27.7)	14.8 (13.0, 16.8)	10.9 (9.4, 12.5)
5–17 years	3.6 (3.2, 4.1)	2.1 (1.7, 2.5)	4.0 (2.3, 6.9)	2.6 (1.2, 5.5)	2.8 (2.3, 3.4)	1.9 (1.5, 2.3)
18–39 years	3.5 (3.1, 3.8)	2.4 (2.1, 2.7)	4.6 (3.2, 6.6)	3.2 (2, 5.2)	3.1 (2.7, 3.5)	2.4 (2.1, 2.7)
40–64 years	10.5 (9.9, 11.0)	7.7 (7.3, 8.2)	12.3 (10.0, 15.1)	9.7 (7.5, 12.5)	11.1 (10.5, 11.8)	8.9 (8.3, 9.4)
65–74 years	23.6 (21.9, 25.5)	17.6 (16.1, 19.2)	26.9 (19.9, 36.4)	21.6 (14.8, 31.6)	22.8 (21.0, 24.8)	17.4 (15.9, 19.0)
75–84 years	31.8 (29.3, 34.5)	23.9 (21.8, 26.3)	36.0 (26.0, 50.0)	27.4 (18, 41.7)	33.4 (30.6, 36.6)	25.3 (22.9, 27.9)
≥85 years	61.5 (55.6, 68.1)	48.9 (43.7, 54.7)	61.0 (40.7, 91.6)	52 (31.8, 85.2)	57.5 (51.7, 63.8)	45.5 (40.6, 50.9)
Total	10.5 (10.2, 10.8)	7.6 (7.3, 7.9)	12.4 (11.0, 14.0)	9.5 (8.1, 11.1)	10.8 (10.4, 11.2)	8.3 (8, 8.7)

Abbreviations: PCV7, PCV10, and PCV13, the 7-valent, 10-valent, and 13-valent pneumococcal conjugate vaccine, respectively.

Table 4
Incidence of invasive pneumococcal disease according to age-group and pneumococcal conjugate vaccine (PCV) program periods in British Columbia, 2002–2018.

Age group	Incidence per 100,000 population (95% Confidence interval)					
	Pre-PCV baseline period		PCV7 period		PCV13 period	
	Overall IPD	Confirmed IPD	Overall IPD	Confirmed IPD	Overall IPD	Confirmed IPD
0–4 years	45.0 (38.5, 52.7)	34.3 (28.7, 41.1)	16.8 (14.8, 19)	13.4 (11.6, 15.4)	8.8 (7.6, 10.2)	7.1 (6.0, 8.4)
5–17 years	4.5 (3.4, 5.9)	3.0 (2.1, 4.2)	2.8 (2.4, 3.4)	2.4 (1.9, 2.9)	3.4 (2.9, 3.9)	2.9 (2.5, 3.4)
18–39 years	2.7 (2.1, 3.5)	1.9 (1.4, 2.6)	4.9 (4.4, 5.3)	3.8 (3.5, 4.3)	3.8 (3.5, 4.2)	3.5 (3.2, 3.9)
40–64 years	6.1 (5.1, 7.2)	3.8 (3.1, 4.6)	11.8 (11.1, 12.5)	8.9 (8.4, 9.5)	10.4 (9.9, 11.0)	9.0 (8.6, 9.5)
65–74 years	11.4 (8.8, 14.8)	5.7 (3.9, 8.3)	15.4 (13.8, 17.1)	11.6 (10.3, 13.2)	16.7 (15.4, 18.0)	14.0 (12.9, 15.2)
75–84 years	23.9 (19.2, 29.9)	11.0 (8.0, 15.3)	20.3 (18.1, 22.7)	14.8 (13.0, 17.0)	21.8 (19.9, 24.0)	18.4 (16.7, 20.4)
≥85 years	28.2 (19.7, 40.3)	15.0 (9.2, 24.5)	36.9 (32.1, 42.5)	28.5 (24.3, 33.5)	35.7 (31.9, 39.8)	30.1 (26.7, 34.0)
Total	8.3 (7.7, 9.0)	5.3 (4.7, 5.8)	9.8 (9.4, 10.1)	7.5 (7.2, 7.8)	9.2 (8.9, 9.5)	7.9 (7.6, 8.2)

Abbreviations: PCV7, PCV10, and PCV13, the 7-valent, 10-valent, and 13-valent pneumococcal conjugate vaccine, respectively.

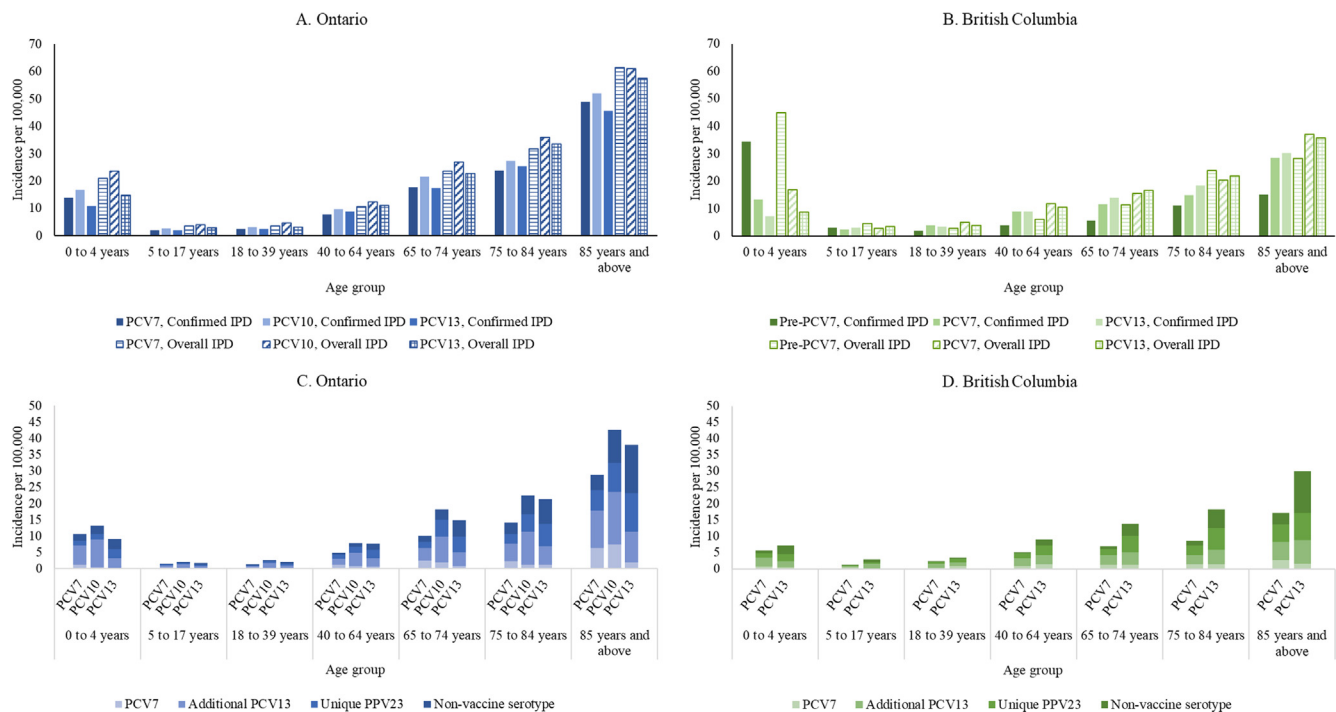


Fig. 2. Age group-specific incidence of invasive pneumococcal disease (IPD) according to pneumococcal conjugate vaccine (PCV) program periods: (A) Overall and confirmed IPD in Ontario, 2005–2018 (B) Overall and confirmed IPD in British Columbia, 2002–2018 (C) Serotype-specific confirmed IPD in Ontario, 2007–2018 (D) Serotype-specific confirmed IPD in British Columbia, 2007–2018.

tional PCV13 serotypes had the highest incidence rate during PCV7 and PCV10 program periods, and non-vaccine serotypes had the highest rate during PCV13 program period. In BC; additional PCV13 serotypes had the highest incidence rate during PCV7 pro-

gram periods and non-vaccine serotypes had the highest incidence rate during PCV13 program period in children aged 0–4 years (Fig. 2D, Supplementary Table 4).

4. Discussion

Our findings suggest that the burden of invasive pneumococcal disease remains high in Canada, even after eight years of a national pediatric PCV13 program.

The burden of confirmed IPD across all age groups remained relatively stable in Ontario during the entire study period 2005–2018, and was 10.5 per 100,000 in 2018. The incidence rate of confirmed IPD in BC has varied, with a peak in 2007, followed by a decline for three years; the decline has reversed recently, and the rate was 12.0 per 100,000 in 2018. The observed peak in 2007 is attributed to two outbreaks of serotype 5, not included in PCV7, among impoverished and drug-using populations [29,30], and likely resulted from serotype replacement caused by PCV7 program implementation [31]. We observed an increase in the rate of IPD by unique PPV23 (non-PCV13) and non-vaccine serotypes from 2007 to 2018 in both provinces, which may explain the unchanged burden of IPD in Ontario or the recent increase in BC given the use of PCV13 since 2010 to reduce the disease burden. Previous studies in Ontario and BC have also reported an increase in the incidence of IPD by serotypes 3, 19A, 7F and 22F during our study period [10,21]. The incidence of total IPD across PCV program periods seemed unchanged with the introduction of PCV programs in our study. However, the total IPD incidence across all age groups for an entire PCV program period does not take into account the yearly changes in the IPD incidence or serotype distribution. It is likely that reductions in the incidence of PCV7 serotypes after introduction of PCV7 were largely offset by an increase in the incidence of additional PCV13, unique PPV23 or non-vaccine serotypes during subsequent PCV10 and/or PCV13 program periods as suggested by Fig. 1C and Fig. 1D. While the efficiency of IPD reporting may have had increased over the period of our study, it is unlikely that such improvement can be attributed to the observed apparently unchanged total IPD incidence across PCV program periods. Of note, pneumococcal vaccination (PPV23) coverage in adults aged ≥ 65 years nationally remains lower than the national coverage goal of 80% in this population; the reported uptake of pneumococcal vaccine remained approximately 40% during 2006 through 2016, and was estimated to be 58% from the latest survey 2018–2019 [32]. Suboptimal PPV23 uptake, together with an increase in both additional PCV13 IPD and unique PPV23 IPD incidence during our study period, suggest that PPV23 may not have the desired level of effect in reducing IPD burden in older adults. The national pneumococcal vaccination coverage in children by two years of age is also below the national coverage goal of 95% [33]; around 80% of children were reported to have received pneumococcal vaccine during 2013–2017, with 84% vaccinated in 2019 [34]. Previous studies have shown an inverse relationship between local pediatric dose-specific PCV7 vaccination rate and indirect protection against IPD in adults or undervaccinated children [35–37]. Additionally, breakthrough PCV7 IPD in children aged < 5 years with incomplete or complete PCV7 or PCV13 dose schedule have been reported previously [38,39]. We also observed an increasing trend in the incidence of PCV7 IPD over the PCV13 period, notably in BC, which may have been caused by breakthrough infections in young.

Our incidence rates of confirmed IPD from surveillance data in 2018 for both provinces (10.5 per 100,000 in Ontario and 12.0 per 100,000 in BC) are higher than the rates reported in other settings. The 2018 IPD burden from USA Active Bacterial Core Surveillance shows overall IPD rates in all age groups decreased from 24.1 per 100,000 people in 1998 to 9.6 per 100,000 people in 2018 [40]. IPD reported to the National Notifiable Disease Surveillance System (NNDSS) in Australia also shows a decrease from 9.1 per 100,000 in 2001 to 6.3 per 100,000 in 2015 before increasing to 8.1 per 100,000 in 2018 [41]. The USA follows a 3 + 1 schedule and Aus-

tralia follows a 3 + 0 schedule, but Canada and most European countries follow a 2 + 1 schedule. The reasons behind the differences between our rates and the rates in USA and Australia remain unknown. Previously, it was reported that USA did not have an increase in IPD caused by non-vaccine serotypes in young children and older adults compared to other high income countries, including UK and Canada both with similar dose schedule; none of the suggested factors such as differences in sampling in surveillance, transmission dynamics, age structure, vaccine dose schedules and uptake, population risk factors and pathogen evolution could individually explain the difference [42]. However, an increase in the proportion of non-vaccine serotypes across all age groups in high-income countries, including USA, Australia and certain European countries has been recently reported suggesting partial replacement [43]. A similar increase in non-PCV13 IPD in hospitalized children aged < 5 years during post-PCV13 period was observed in USA, Canada and European countries [44].

We used surveillance and health administrative data to address underreporting by laboratory-based surveillance systems reported in previous studies [9,10] and approximate the overall burden of IPD using a sensitive ICD-10-CA defined case definition. Possible IPD cases from administrative databases contributed to approximately one-fourth of overall IPD cases (24% in Ontario and 19% in BC). Reporting of cases depends on varying factors, including disease awareness, health care seeking behaviours, changes in IPD case definitions, the severity of illness, clinical practice, laboratory testing methods and reporting behaviour [11]. The magnitude of confirmed IPD underreporting in the Canadian context remains unknown and should be investigated in future studies. Very few studies have studied underreporting in IPD surveillance. A previous Australian study determining whether all diagnosed IPD cases were reported estimated that at least 17% of laboratory-confirmed IPD cases were missed during two initial years of IPD surveillance [45]. Quattrone et al recently reported substantial incompleteness in three data sources, with the hospitalization data performing best compared to IPD and microbiological surveillance data in Italy [46]. Similarly, in Canada, differences in decentralized health care, data systems, and vaccination programmes across jurisdictions make it difficult to compare data across provinces. While an enhanced IPD surveillance system linking laboratory and epidemiologic data piloted in 2011 in Canada seemed promising in better capturing IPD and understanding the trends [47], an enhanced IPD surveillance has not been implemented yet.

The strength of this study is that we estimated the population-based burden of invasive pneumococcal disease across all age groups in 20 million people over 14 years in Ontario and 17 years in BC. Using multiple health administrative databases along with surveillance data enabled us to better gauge the comprehensive burden of IPD by accounting for the possible IPD cases that may not have been captured by the surveillance system.

Our study had a number of limitations. Diagnostic and laboratory practices to identify a patient with IPD may vary among physicians in Ontario and BC. Our study used administrative databases and relied on the use of diagnostic codes by physicians. As a result, it has the potential for misdiagnosis/miscoding or misclassification of possible IPD resulting in an overestimation of the burden of overall IPD. In contrast, approximately half of confirmed IPD in both provinces could not be linked to administrative databases suggesting either an underestimation of the burden or possible non-IPD-specific diagnosis (for example, pneumonia) or miscoding during code assignment through reabstraction of clinical documentation by physicians. Of note, coders do not incorporate conditions from diagnostic test results during code assignment [48]. This warrants further investigation in future studies. However, some coding discrepancy in emergency department data has been reported [49]. There is also the potential for possible underreport-

ing because of the use of antibiotics prior to specimen collection. We used hospital discharge date as the index date to identify recurrent episodes. As a result, although likely infrequent, any IPD patient with length of stay > 30 days would be counted as having a recurrent episode. Lack of pre-PCV period data in Ontario precluded examining IPD burden from pre-PCV to post-PCV program periods. The lack of emergency department data from BC may have led to an underestimation of possible IPD cases. Serotype information was not available for 21% of confirmed IPD cases in Ontario, which limits generalizability of serotype-specific IPD burden in the province. The trends in the burden of IPD may vary depending on population structure, population distribution of risk factors, local transmission dynamics of pneumococcal serotypes, vaccine coverage, and surveillance systems; thus, our findings may not be generalizable to other jurisdictions.

5. Conclusions

Our findings suggest ongoing substantial burden of IPD in Canada, despite some degree of success with the costly publicly-funded pneumococcal vaccination programs in place for more than a decade. The benefit of the conjugate vaccine is greater in those who are directly getting the vaccine (i.e., children), rather than indirect protection (i.e., adults). We believe the suboptimal PCV vaccine coverage and serotype replacement by PCV vaccines may have also limited the overall gains from the PCV vaccines. This reinforces the need to investigate the reasons to generate evidence if a higher valent PCV program should be considered to augment the reduction in disease burden. Canada could also benefit from strengthening systems, including surveillance system to better monitor the impact of the pneumococcal vaccination program on the burden of IPD.

Ethics approval

ICES is a prescribed entity under Ontario's Personal Health Information Protection Act (PHIPA). Section 45 of PHIPA authorizes ICES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management of, evaluation or monitoring of, the allocation of resources to or planning for all or part of the health system. Projects that use data collected by ICES under section 45 of PHIPA, and use no other data, are exempt from REB review. The use of the data in this project is authorized under section 45 and approved by ICES' Privacy and Legal Office.

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Data availability statement

The dataset from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (e.g., healthcare organizations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [MS has been an investigator on projects funded by GlaxoSmithKline, Merck, Pfizer, Sanofi-Pasteur, Seqirus, Symvivo and VBI Vaccines. All funds have been paid to his institute, and he has not received any personal payments. SKM is co-PI on a project funded by Pfizer that is unrelated to this manuscript, has served on an advisory board for Pfizer, and has received speaker fees from GlaxoSmithKline. The Centre for Vaccine Preventable Diseases is operated by the Dalla Lana School of Public Health, which receives funding from government, philanthropic, not for profit and private sector organization, including vaccine manufacturers. This includes a donation from Merck to the institution that supports the salary of SF. SF does not receive funding directly from Merck or any personal payment or direct funds from vaccine manufacturers to support her research. Other authors declare no conflicts of interest.].

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2021.11.032>.

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