OPEN ACCESS

Original research

Indirect impact of childhood 13-valent pneumococcal conjugate vaccine (PCV13) in Canadian older adults: a Canadian Immunization Research Network (CIRN) retrospective observational study

Sharifa Nasreen ,[1,2,3,4] Jun Wang,[3,5] Fawziah Marra,[6] Jeffrey C Kwong,[1,2,3,5,7,8] Allison McGeer,[1,2,9,10,11] Manish Sadarangani,[12,13] Sarah E Wilson,[1,2,3,5] Shaza A Fadel [1,2]

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/thorax-2023-220377).

For numbered affiliations see end of article.

Correspondence to
Dr Shaza A Fadel, University of Toronto Dalla Lana School of Public Health, Toronto, ON M5T 3M7, Canada; shaza.fadel@utoronto.ca

FM and SAF are joint senior authors.

Received 17 April 2023
Accepted 19 January 2024
Published Online First 15 February 2024

ABSTRACT

Background 13-valent pneumococcal conjugate vaccine (PCV13) has been part of publicly funded childhood immunisation programmes in Ontario and British Columbia (BC) since 2010. We assessed the indirect impact of infant PCV13 programmes on invasive pneumococcal disease (IPD) and all-cause pneumonia hospitalisation in older adults (aged ≥65 years) using a retrospective observational study.

Methods We extracted monthly IPD and all-cause pneumonia cases from laboratory and health administrative databases between January 2005 and December 2018. Using a quasi-experimental difference-in-differences design, we calculated the ratio of risk ratios (RRRs) using incidence rates of IPD or all-cause pneumonia cases before (pre-PCV13 period) and after (PCV13 period) 2010 with rates of fractures as controls.

Results The rates of all IPD or PCV serotype-specific IPD for older adults in both Ontario and BC did not change in 8 years after childhood PCV13 programme implementation. All-cause pneumonia increased in Ontario (RRR 1.38, 95% CI 1.11 to 1.71) but remained unchanged in BC.

Conclusions Indirect community protection of older adults from hospitalisation with pneumococcal disease stalled despite maturation of childhood PCV13 vaccination programmes in two Canadian provinces.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Older adults have benefited from community protection provided by childhood 7-valent pneumococcal conjugate vaccine (PCV7) programmes, reducing severe outcomes such as hospitalisation for pneumonia.

⇒ Invasive pneumococcal disease (IPD) incidence in older adults decreased in Ontario but increased in British Columbia (BC) after PCV13 replaced earlier conjugated vaccines in the routine childhood programme.

⇒ It remains unknown if after maturation, childhood PCV13 vaccination programmes benefited older adults in reducing IPD and all-cause pneumonia hospitalisation in Ontario and BC.

WHAT THIS STUDY ADDS

⇒ Using 8 years of continuous data and a quasi-experimental difference-in-differences design, this study quantified the population-level indirect benefit of community protection of publicly funded childhood PCV13 programme on pneumococcal disease burden in older adults.

⇒ This study found that 8 years of paediatric PCV13 programmes in Ontario and BC did not reduce incidence rates of pneumococcal disease (IPD or all-cause pneumonia) in the older populations in either province.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlights the importance of ongoing surveillance to monitor serotypes in the Canadian population to aid evidence-based decision-making and the need for an improved approach to the prevention of IPD in older adults given the low uptake of 23-valent pneumococcal polysaccharide vaccine and the potential benefit of higher-valency PCVs recently made available in Canada.

INTRODUCTION

Adults aged ≥65 years are more susceptible to severe outcomes from infectious diseases because of immunosenescence and chronic comorbidities, such as chronic obstructive pulmonary disease, asthma, diabetes and chronic heart disease. This also includes an increase in the risk of pneumococcal disease and its more severe outcomes, invasive pneumococcal disease (IPD) such as bacteraemia, meningitis and bacteraemic pneumonia.[1 2] Nasopharyngeal carriage plays a key role in pneumococcal disease causation and transmission, with children being the major reservoir of *Streptococcus pneumoniae*.[3 4]

Routine vaccination of infants and young children with pneumococcal conjugate vaccines (PCVs) has led to community protection with significant decreases in nasopharyngeal carriage rates, hospitalised pneumonia and IPD in several high-income and low-income countries, for all age

Check for updates

To cite: Nasreen S, Wang J, Marra F, *et al*. *Thorax* 2024;**79**:861–869.

groups including older adults.[5–8] In a meta-analysis of indirect effects of childhood PCV programmes on IPD for older adults, maturation of a childhood 13-valent PCV (PCV13) programme was predicted to result in a 50% and 90% reduction in IPD caused by the additional serotypes in PCV13 approximately 4 years and 10 years, respectively, after vaccine introduction.[8] Publicly funded childhood PCV programmes with successively higher-valency PCVs, PCV7, PCV10 and PCV13, have been in use in Canada for almost two decades. However, IPD rates have not been consistently declining. A study from Ontario reported substantial declines in pneumonia hospitalisations in older adults, but this study assessed the impact of PCV13 only 3 years after its introduction before the programme had matured.[9]

In our previous study covering two provinces in Canada, we observed a decreased incidence of IPD caused by serotypes covered by PCV7, but the incidence caused by serotypes unique to 23-valent pneumococcal polysaccharide vaccine (PPV23) (ie, serotypes not present in PCV13) and non-vaccine serotypes increased in older adults in both provinces during 2007–2018.[10] We also observed a decrease in the incidence of outpatient and inpatient all-cause community-acquired pneumonia during the PCV13 period in Ontario and British Columbia (BC) in older adults.[11]

The benefit of mature PCV13 childhood vaccination programmes on community protection for older adults in a Canadian context is unknown. In this study, we examined the impact of paediatric PCV13 vaccination programmes on IPD and all-cause pneumonia in older adults in two large Canadian provinces.

METHODS

Study population, setting and design

We conducted a population-based retrospective observational study in Ontario and BC between 2005 and 2018 to estimate the indirect impact of 8 years of childhood PCV13 programmes on IPD and hospitalised pneumonia in adults aged ≥65 years. Ontario is the largest province with approximately 15 million population, whereas BC is the third largest province with a population of approximately 5 million. These two provinces with high-quality data represent different regions of the country and comprise 53% of the Canadian population.

There is no established standard for defining the maturation of pneumococcal vaccination programmes, but we defined the programmes in Canada as mature based on previous studies.[12] The PCV programmes were publicly funded in Ontario and BC at somewhat different times.[13] In BC, PCV7 was introduced in September 2003 and replaced by PCV13 in June 2010, whereas in Ontario, PCV7 was introduced in January 2005, and it was replaced by PCV10 in October 2009, and then PCV10 was replaced by PCV13 in November 2010. Publicly funded PCV13 has been available to immunocompromised adults aged ≥50 years in Ontario since December 2014[14] and to adults with a stem cell transplant (February 2013) or HIV infection (March 2015) in BC.[15] Publicly funded PPV23 has been available for adults aged ≥65 years since 1996 in Ontario and 1998 in BC; however, PPV23 uptake remains low (48% for males and 60% for females in 2021).[16]

We employed a quasi-experimental difference-in-differences (DID) study design that can be used to estimate potential causal effects of an intervention on observed outcomes in settings where randomised controlled trials are infeasible.[17 18]

Data sources

We obtained data on laboratory-confirmed IPD, including IPD serotype, from Ontario's integrated Public Health Information System and the BC Centre for Disease Control Public Health Laboratory data. Hospitalisations for all-cause pneumonia and two negative control outcomes, fractures and skin and soft tissue infections (SSTIs), were identified from the Canadian Institute for Health Information's Discharge Abstract Database (DAD).[19] 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.[20] Data were analysed separately in Ontario and BC using similar methods. Datasets were linked using unique identifiers; Ontario datasets were analysed at ICES, and BC datasets were analysed at Population Data BC.

Outcomes

A laboratory-confirmed IPD case was defined as isolation of *S. pneumoniae* and/or identification of *S. pneumoniae* DNA from a normally sterile site (eg, blood, cerebrospinal fluid, synovial or peritoneal fluid and bone), excluding the middle ear.[21 22] IPD cases with serotype information were grouped into four categories based on serotypes covered by PCVs: (1) PCV7 (4, 6B, 9V, 14, 18C, 19F and 23F), (2) additional PCV13 (serotypes not present in PCV7: 1, 3, 5, 6A, 7F and 19A), (3) unique PPV23 (11 serotypes not present in PCV13: 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F and 33F) and (4) non-vaccine (serotypes not included in PCV13 or PPV23).

We used fractures and SSTIs as negative control outcomes because pneumococcal vaccination is not expected to impact or be causally related to these outcomes; these outcomes capture secular, but still distinct, trends in healthcare system use during the study period.

Cases of all-cause pneumonia, fractures and SSTIs assigned as the primary or secondary diagnosis were identified using diagnostic codes from the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada (ICD-10-CA)[23] in DAD (online supplemental table S1). We included all-cause pneumonia hospitalisation without a concurrent IPD diagnosis (ie, included non-invasive pneumonia). Concurrent IPD diagnoses were identified using the following: pneumococcal meningitis (ICD-10-CA: G00.1), pneumococcal septicaemia (ICD-10-CA: A40.3), pneumococcus elsewhere (eg, infective pericarditis, acute peritonitis, puerperal sepsis and congenital pneumonia) (ICD-10-CA: B95.3) or pneumococcal arthritis and polyarthritis (ICD-10-CA: M00.1). We included fractures and SSTIs without concurrent pneumonia or IPD.

We removed duplicate records using unique identifiers and the admission date in hospitalised patients (ie, DAD database). To identify recurrent cases, we used the discharge date (DAD) to account for the length of hospital stay. We considered IPD and SSTI episodes >30 days and all-cause pneumonia episodes >90 days to be separate episodes and included them. For fracture, we included the first diagnosis.

Statistical analysis

The study period was divided into two intervals: (1) pre-PCV13 period and (2) PCV13 period. Age was categorised into the following groups: ≥65 years, 65–74 years, 75–84 years and ≥85 years. For each age group, we estimated annual and period-specific incidence rates of IPD, all-cause pneumonia, fractures and SSTIs using Poisson regression models, with population estimates from Statistics Canada as the offset parameter.[24]

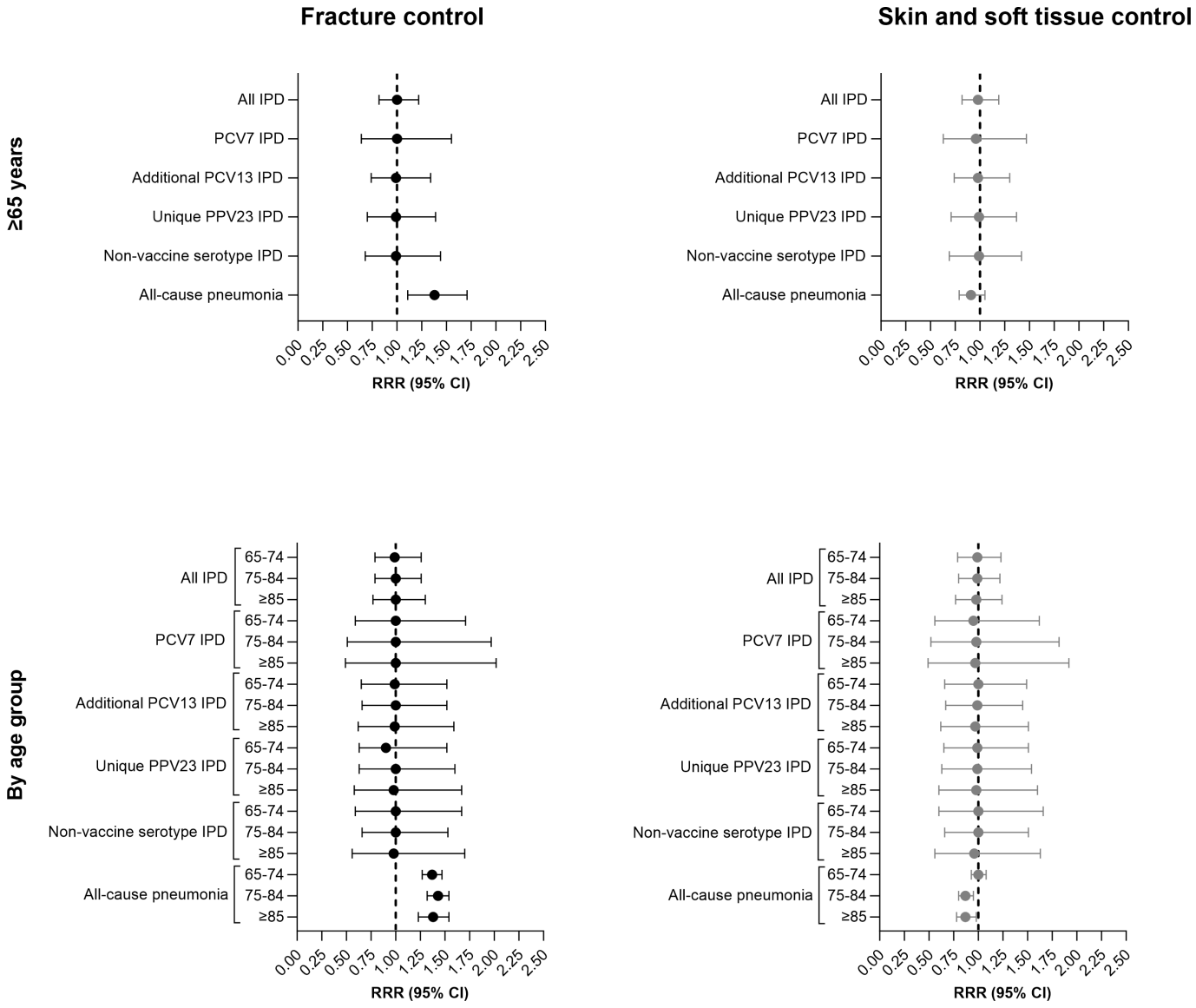

Figure 1 Indirect impact of 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease and all-cause pneumonia in older adults aged ≥65 years in Ontario, 2005–2018. IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine; RRR, ratio of risk ratio.

For the indirect effect evaluation using the DID method, we used fractures and SSTIs as controls for primary and secondary analyses, respectively. We visually inspected the annual incidence rates for all identified cases to check that the parallel trend assumption for IPD, pneumonia, fractures and SSTIs during the pre-PCV13 period was not violated. The trends were parallel, except in 2007 due to an outbreak of serotype 5 IPD among socioeconomically disadvantaged populations in BC[25 26] (online supplemental figure 1). Thus, the change in the incidence of fractures or SSTIs from the pre-PCV13 period to the PCV13 period was assumed to be a valid counterfactual for the change that would have occurred in the incidence of IPD and all-cause pneumonia in the absence of a publicly funded childhood PCV13 immunisation programme.

In Ontario, we employed propensity score matching with the DID method to select controls with similar characteristics in order to make the common trend assumption more plausible. Propensity scores were computed using logistic regression models using age group, sex, comorbidity using the Charlson comorbidity score, month and year. We used the Greedy method to match three controls for each IPD and two controls for each all-cause pneumonia with a standard deviation of less than 20% in absolute value. We tested the parallel trend assumption in the propensity score matched sample using general linear model regressions with the rate of the outcome as the dependent variable, case/control status and time since PCV13 as independent variables and an interaction between case/control status and time since PCV13. A statistically non-significant coefficient for the interaction term suggested that the parallel trend assumption was held. In BC, we matched three controls for each case by age group, sex, month and year.

We estimated the indirect effect as the ratio of risk ratios (RRRs) (ie, the ratio of 'PCV13 risk ratio' and 'pre-PCV13 risk ratio') to determine whether IPD and all-cause pneumonia incidence increased or decreased for older adults after PCV13 introduction into the childhood immunisation programme compared with the pre-PCV13 period. 'PCV13 risk ratio' was calculated from the ratio of the cumulative incidences of either IPD or

Table 1 Total counts and mean age-specific annual incidence of invasive pneumococcal disease identified from public health laboratory data, and all-cause pneumonia, fractures and skin and soft tissue infections from health administrative data in adults aged ≥65 years in Ontario and British Columbia, Canada, 2005–2018

	Invasive pneumococcal disease		All-cause pneumonia		Fracture		Skin and soft tissue infection	
Age group, years	No.	Incidence/100 000 population (95% CI)	No.	Incidence/100 000 population (95% CI)	No.	Incidence/100 000 population (95% CI)	No.	Incidence/100 000 population (95% CI)
Ontario								
65–74	2669	17.7 (16.8 to 18.8)	39 262	261.0 (249.8 to 272.7)	64 599	429.4 (417.5 to 441.7)	36 113	240.1 (235.5 to 244.7)
75–84	2244	25.0 (23.5 to 26.6)	50 893	567.5 (546.2 to 589.7)	101 826	1135.5 (1110.3 to 1161.3)	39 048	435.5 (427.5 to 443.6)
≥85	1662	46.9 (43.7 to 50.4)	41 868	1181.7 (1132.7 to 1232.7)	102 043	2880.0 (2816.0 to 2945.4)	28 244	797.1 (780.0, to 814.7)
Overall (≥65)	6575	23.9 (22.9 to 24.9)	132 023	479.2 (458.9 to 500.3)	268 468	974.4 (929.0 to 1021.9)	103 405	375.3 (364.0 to 387.0)
British Columbia								
65–74	760	13.6 (12.1 to 15.2)	11 441	204.1 (193.4 to 215.5)	24 846	443.3 (412.3 to 476.7)	7305	130.3 (122.9 to 138.2)
75–84	554	17.3 (15.6 to 19.1)	13 684	427.1 (401.8 to 454.1)	32 686	1020.2 (945.2 to 1101.3)	7209	225.0 (209.0 to 242.3)
≥85	396	29.9 (26.5 to 33.7)	10 388	784.2 (738.5 to 832.8)	34 320	2591.0 (2417.8 to 2776.6)	5298	400.0 (360.8 to 443.5)
Overall (≥65)	1710	16.9 (15.6 to 18.3)	35 513	350.5 (330.3 to 371.9)	91 852	906.5 (838.2 to 980.3)	19 812	195.5 (182.1 to 210.0)

all-cause pneumonia and either fractures or SSTIs during the PCV13 period; 'pre-PCV13 risk ratio' was calculated from the ratio of the cumulative incidences of IPD or all-cause pneumonia and fractures or SSTIs during the pre-PCV13 period. We analysed monthly incidence data from January 2005 to December 2018 for each disease outcome, with the number of IPD, all-cause pneumonia, fracture and SSTI outcomes for those aged ≥65 years overall and by age group using Poisson regression models with the log link function and population as the offset. Monthly serotype group-specific IPD incidence was available from January 2005 to December 2018 in BC and only from January 2007 to December 2018 in Ontario. In Ontario, using the propensity score matched DID analysis, we accounted for the PCV10 programme by incorporating PCV10 fixed effects in the regression models by including a separate binary variable; we also accounted for publicly funded PCV13 for immunocompromised adults aged ≥50 years since December 2014 by including a separate binary variable. All analyses were conducted using SAS V.9.4 (SAS Institute) software. All tests were two sided and used $p<0.05$ as the level of statistical significance.

RESULTS

The total number of identified cases and the calculated mean age-specific incidence rates for IPD, all-cause pneumonia and the two control groups in each of the provinces are shown in table 1. We identified a total of 6575 IPD, 132 023 all-cause pneumonia, 268 468 fracture and 103 405 SSTI cases in Ontario during 2005–2018 with mean annual incidence rates per 100 000 population of 23.9 for IPD, 479.2 for all-cause pneumonia, 974.4 for fracture and 375.3 for SSTI. In BC, we identified a total of 1710 IPD, 35 513 all-cause pneumonia, 91 852 fracture and 19 812 SSTI cases, with mean annual incidence rates per 100 000 population of 16.9 for IPD, 350.5 for all-cause pneumonia, 906.5 for fracture and 195.5 for SSTI. Annual incidence by age group is shown in online supplemental figure 1 and online supplemental table S2.

Serotype information were available for 4591 IPD (79% out of 5812) cases during 2007–2018 in Ontario, with a mean annual incidence per 100 000 population of 1.5 for PCV7 IPD, 5.7 for additional PCV13 IPD, 5.6 for unique PPV23 IPD and 6.0 for non-vaccine serotype IPD among adults aged ≥65 years (online supplemental figure 2, table 2, online supplemental table S3). In BC, serotype information were available for 1686 IPD (99% of 1710) cases during 2005–2018; the mean annual incidence per 100 000 population of IPD according to vaccine serotype was 2.1 for PCV7 IPD, 4.7 for additional PCV13 IPD, 5.4 for unique PPV23 IPD and 4.5 for non-vaccine serotype IPD among adults aged ≥65 years (table 2).

Indirect effect of childhood PCV13 immunisation on IPD and all-cause pneumonia

Ontario

The propensity score matched DID analytic sample for all IPD included 5811 IPD and 17 416 matched fracture controls and 5783 IPD matched with 17 244 SSTI controls. For all-cause pneumonia, the sample included 129 791 all-cause pneumonia and 261 273 matched fracture controls and 106 652 all-cause pneumonia matched with 103 354 SSTI controls. Tests for parallel trend assumption suggested that during the pre-PCV13 period, the parallel trend assumption was not violated using both control conditions, except for the additional PCV13 IPD and SSTI control (data not shown).

In the primary analysis, using fracture as the control condition, we did not observe any statistically significant changes in trends of all IPD or serotype-specific IPD in Ontario for adults aged ≥65 years (figure 1, table 3, online supplemental table S4). Similar findings were observed in the secondary analysis using SSTI as the control condition. For all-cause pneumonia, we observed a statistically significant increase in all-cause pneumonia incidence in adults aged ≥65 years and across all age groups with fracture used as controls; however, a statistically significant

Table 2 Total counts and mean age-specific annual incidence of invasive pneumococcal disease identified from public health laboratory data according to vaccine serotype group in older adults in Ontario and British Columbia, Canada, 2005–2018

	PCV7 IPD		Additional PCV13 IPD		Unique PPV23 IPD		Non-vaccine serotype IPD	
Age group, years	No.	Incidence/100 000 population (95% CI)	No.	Incidence/100 000 population (95% CI)	No.	Incidence/100 000 population (95% CI)	No.	Incidence/100 000 population (95% CI)
Ontario (2007–2018)								
65–74	160	1.2 (1.0 to 1.4)	595	4.5 (4.0 to 5.0)	576	4.3 (3.9 to 4.8)	552	4.2 (3.7 to 4.6)
75–84	112	1.4 (1.2 to 1.7)	468	6.0 (5.3 to 6.7)	454	5.8 (5.2 to 6.5)	511	6.6 (5.9 to 7.3)
≥85	99	3.1 (2.6 to 3.8)	329	10.4 (9.0 to 11.9)	338	10.6 (9.4 to 12.1)	397	12.5 (11.1 to 14.2)
Overall (≥65)	371	1.5 (1.4 to 1.7)	1392	5.7 (5.3 to 6.2)	1368	5.6 (5.3 to 6.0)	1460	6.0 (5.6 to 6.5)
British Columbia (2005–2018)								
65–74	101	1.8 (1.3 to 2.6)	220	3.9 (3.3 to 4.7)	253	4.5 (3.8 to 5.3)	176	3.1 (2.4 to 4.1)
75–84	69	2.2 (1.4 to 3.2)	149	4.7 (4.1 to 5.3)	187	5.8 (4.5 to 7.5)	144	4.5 (3.2 to 6.3)
≥85	41	3.1 (1.9 to 5.1)	103	7.8 (5.8 to 10.5)	107	8.1 (6.5 to 10.1)	136	10.3 (8.1 to 13.0)
Overall (≥65)	211	2.1 (1.5 to 2.9)	472	4.7 (4.1 to 5.3)	547	5.4 (4.6 to 6.3)	456	4.5 (3.5 to 5.8)

IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine.

decrease in all-cause pneumonia was observed in adults aged ≥75 years using SSTI controls. The effect estimates (RRRs) with and without (data not shown) accounting for publicly funded PCV13 for immunocompromised adults aged ≥50 years and the brief PCV10 programme were similar.

British Columbia

The age group and sex matched DID analytic sample for all IPD included 1677 IPD and 5031 matched fracture controls and 1676 IPD matched with 5026 SSTI controls. For all-cause pneumonia, the sample included 32 408 all-cause pneumonia and 97 251 matched fracture controls and 32 402 all-cause pneumonia matched with 97 158 SSTI controls.

In the primary analysis, using fracture as the control condition, we did not observe any statistically significant changes in trends of all IPD, serotype-specific IPD or all-cause pneumonia incidence after PCV13 programme implementation in adults aged ≥65 years (figure 2, table 3, online supplemental table S5). Similar findings were observed in the secondary analysis using SSTI as the control condition.

DISCUSSION

We analysed 8 years of data on cases of IPD and all-cause pneumonia requiring hospitalisation representative of two large Canadian provinces before and after the integration of PCV13 into routine childhood vaccination programme. We showed that publicly funded mature childhood PCV13 immunisation programme (2+1 schedule) in Ontario and BC did not reduce IPD or all-cause pneumonia hospitalisation among older adults in either province. Rates of all-cause pneumonia increased in

Table 3 Indirect impact of PCV13 on invasive pneumococcal disease and all-cause pneumonia in older adults aged ≥65 years in Ontario and British Columbia, 2005–2018*

	Fracture control				Skin and soft tissue infection control			
	Incidence per 100 000				Incidence per 100 000			
Outcome	Case, pre-PCV13, PCV13	Control, pre-PCV13, PCV13	Ratio of risk ratios (95% CI)	P value	Case, pre-PCV13, PCV13	Control, pre-PCV13, PCV13	Ratio of risk ratios (95% CI)	P value
Ontario								
All IPD	21.2, 22.2	63.3, 66.7	1.00 (0.82 to 1.22)	0.9794	21.0, 21.7	62.0, 65.1	0.98 (0.82 to 1.19)	0.8642
PCV7 IPD	2.6, 0.9	7.9, 2.6	1.00 (0.64 to 1.55)	1.0000	2.6, 0.8	7.6, 2.5	0.96 (0.63 to 1.47)	0.8644
Additional PCV13 IPD	4.7, 5.8	14.1, 17.4	0.99 (0.74 to 1.34)	0.9729	4.7, 5.5	13.9, 16.6	0.98 (0.74 to 1.30)	0.9144
Unique PPV23 IPD	2.6, 5.0	7.8, 15.1	0.99 (0.70 to 1.39)	0.9403	2.7, 4.9	7.9, 14.8	0.99 (0.71 to 1.37)	0.9371
Non-vaccine serotype IPD	2.5, 5.9	7.5, 17.7	0.99 (0.68 to 1.44)	0.9666	2.5, 5.9	7.4, 17.8	0.99 (0.69 to 1.42)	0.9508
All-cause pneumonia	391.6, 507.9	974.9, 918.4	1.38 (1.11 to 1.71)	0.0041	376.9, 366.8	344.1, 366.8	0.91 (0.79 to 1.05)	0.2156
British Columbia								
All IPD	15.4, 17.1	46.3, 51.2	1.00 (0.83 to 1.20)	0.9794	15.4, 17.1	46.1, 51.2	1.00 (0.83 to 1.19)	0.9678
PCV7 IPD	3.5, 1.4	10.5, 4.1	0.99 (0.67 to 1.45)	0.9476	3.5, 1.4	10.6, 4.1	1.00 (0.68 to 1.47)	0.9882
Additional PCV13 IPD	4.9, 4.5	14.8, 13.5	1.00 (0.76 to 1.31)	1.00	4.9, 4.5	14.7, 13.5	0.99 (0.76 to 1.30)	0.9635
Unique PPV23 IPD	4.3, 5.8	12.9, 17.5	1.00 (0.76 to 1.32)	1.00	4.3, 5.8	12.9, 17.5	1.00 (0.76 to 1.31)	0.9863
Non-vaccine serotype IPD	2.3, 5.4	6.8, 16.3	1.00 (0.72 to 1.39)	1.00	2.3, 5.4	6.8, 16.3	1.00 (0.72 to 1.39)	1.00
All-cause pneumonia	330.0, 315.0	990.2, 945.0	1.00 (0.92 to 1.09)	0.9932	329.4, 315.3	986.6, 945.9	1.00 (0.92 to 1.09)	0.9664

*Invasive pneumococcal disease identified from public health laboratory data and pneumonia identified from health administrative data.
IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine.

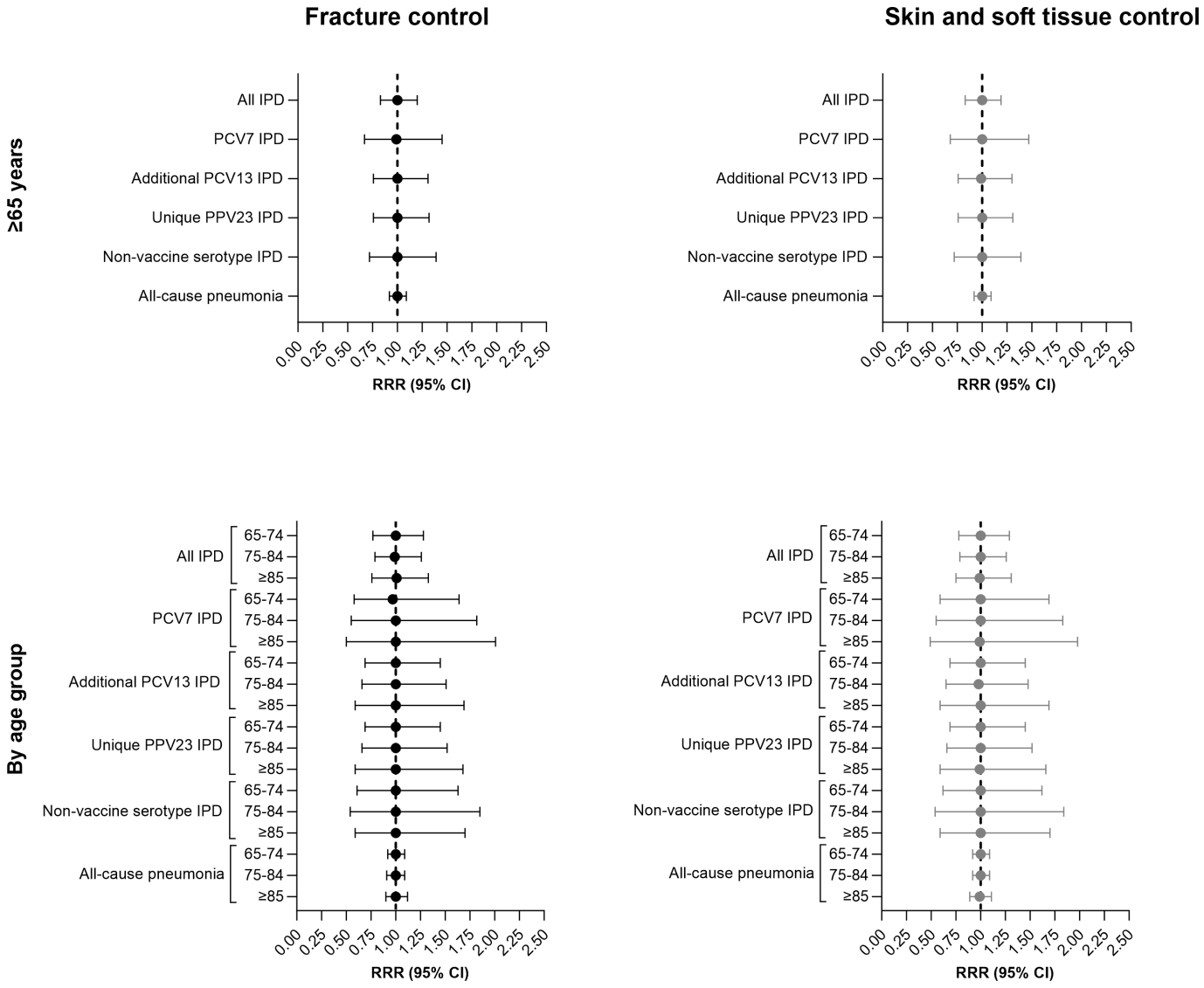

Figure 2 Indirect impact of 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease and all-cause pneumonia in older adults aged ≥65 years in British Columbia, 2005–2018. IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine; RRR, ratio of risk ratio.

Ontario in all older adult age groups. These findings collectively suggest that the indirect benefits of childhood PCV vaccination programmes in older adults may have been attenuated by a lower impact of community immunity for strains in PCV13 and not in PCV7 and by a failure of adult PPV23 programmes to reduce the incidence of PPV23 strains (which might be due to either or both of the limited uptake of PPV23 in older adults or waning of protection from PPV23 in these populations).

Indirect effects of PCV on older populations depend on high PCV coverage among children and the longer duration of PCV programme implementation.[7] A previous study predicted that 90% reduction in IPD caused by PCV7 serotypes in adults aged ≥65 years could be achieved in an average of 8.9 (credible interval 7.9–10.3) years following the introduction of PCV7 vaccination.[8] Modelling predicted a 90% reduction in the additional PCV13 serotype IPD in older adults in an average of 10.3 (credible interval 6.4–20.7) years from the time when PCV7 was replaced by PCV13.[8] However, neither Ontario nor BC had the PCV13 programme for this duration during our study period to experience discernible level of reduction. In addition, up-to-date relevant PCV (PCV7, PCV10 and PCV13) vaccine coverage in children (ie, valid doses according to the vaccine schedule for age) aged 7 years was lower in Ontario, 74%–80% during 2014–2018,[27] than the up-to-date PCV7 or PCV13 vaccine coverage in 2-year-olds in BC, 82%–86% during 2011–2018.[28] These may explain the observed lack of indirect effect against IPD in both provinces.

Because pneumococcal vaccines target only some of the more than 100 pneumococcal serotypes, concerns have been raised that non-vaccine serotypes could increase in prevalence and reduce the benefits of vaccination. Nationally, among Canadian older adults during 2011–2015, additional PCV13 serotypes 3, 7F and 19A and unique PPV23 serotype 22F were prevalent vaccine-preventable serotypes with an increase in serotype 3, while serotypes 15A and 23A were prevalent non-vaccine-preventable serotype IPD.[13] We observed no change in the incidence of IPD in older adults in Ontario and BC. This is not surprising in the context of low PPV23 vaccine uptake in Canadian older adults[16]; the lower vaccine effectiveness against IPD, pneumococcal pneumonia and all-cause pneumonia with increasing age; and waning

of protection over time in older adults.[29] Contrary to our findings, increases in IPD caused by non-PCV13 serotypes in older adults have been reported in the UK, European countries and the USA.[8 30–34] Partial replacement by non-vaccine serotypes and increases in unique PPV23 serotype IPD have been observed in other high-income countries.[35 36]

All-cause pneumonia incidence appears to have increased during the PCV13 period in Ontario, which may have resulted from increases in pneumonia caused by PCV13 serotypes 3, 6A and 19A and PPV23 serotypes,[37] as well as from increases in pneumonia caused by other bacterial and non-bacterial pathogens, ageing of the population and increased prevalence of comorbidities.

The strength of this study is that the multijurisdictional analysis allowed us to evaluate the entire population of adults aged ≥65 years in Ontario and BC. We were able to examine the indirect impact of PCV13 vaccine on IPD, PCV serotype-specific IPD and hospitalised all-cause pneumonia in older adults up to more than 8 years since the implementation of the paediatric PCV13 vaccine programme in Ontario and BC.

Our retrospective observational study has some limitations. The lack of validation of diagnostic codes in administrative data may have biased our impact estimates. However, we used diagnostic codes used in previous studies evaluating the impact of PCVs.[9 38] The lack of individual-level pneumococcal vaccination data precluded us from accounting for PCV13 and PPV23 vaccination status in older adults and removing any direct effects imparted by these vaccines. Nationally, the reported uptake of pneumococcal vaccine in adults aged ≥65 years was around 40% from 2006 to 2016 and was 58% during 2018–2019.[39] However, with higher vaccine coverage among children, the assumption is that we would be measuring the indirect impact more than the direct impact of adult vaccination programmes. We accounted for publicly funded PCV13 for immunocompromised adults aged ≥50 years in Ontario that was implemented in December 2014. We were unable to account for confounders such as smoking because of a lack of data. We could employ matching only by age group and sex in BC because of a lack of information on comorbidity in the analytic dataset for this study, and there remains the potential for residual confounding. However, in DID analysis, the covariates do not need to be balanced between the intervention and control groups, and only if a covariate differs between the treatment and control groups and if the relationship between the covariate and the outcome varies over time, then that covariate is considered as a confounder in a DID analysis.[40] Additionally, an absence of selection bias resulting from unobserved characteristics is not testable. The parallel trend assumption was assessed with graphical inspection in BC, and it was assumed that IPD, pneumonia, fracture and SSTI rates trended closely during the pre-PCV13 period. We used monthly counts to model our DID analysis resulting in numerous pre-PCV13 and PCV13 period time points. As such, the parallel trend assumption (unmeasured variables are either time-invariant group attributes or time-varying factors that are group invariant) may not hold across all groups and time points, although it may hold for some groups and time points, and the results should be interpreted with caution.[41] We employed two negative control conditions to account for secular trends in the healthcare system. The impact of PCV13 programme on all-cause pneumonia in Ontario was not comparable between the control conditions suggesting that the SSTI control may not have adequately captured the secular trends and may have been subject to residual confounding.

In conclusion, we observed limited indirect benefit of childhood PCV13 vaccination on pneumococcal disease burden in Canadian older adults even after 8 years of publicly funded childhood PCV13 vaccination programme implementation. Although publicly funded PPV23 has been available to adults aged ≥65 years in Canada since the mid-1990s, its uptake remains low in older adults.[16] Our study would suggest that the decreasing IPD trend has plateaued or reversed and warrants consideration of the potential benefits of immunising older adults with PCV,[42–44] particularly higher-valency vaccines (PCV15 and PCV20) recently authorised and recommended for pneumococcal programmes in Canada[45] or newer products in the pipeline (PCV21 an PCV24). Taking into consideration the current evidence on disease burden and the efficacy, effectiveness, immunogenicity, safety and cost-effectiveness of PCV15 and PCV20, Canada's National Advisory Committee on Immunization has recently provided a strong recommendation for PCV20 for older adults, as well as individuals under 65 years of age with specific risk factors.[45]

Author affiliations
[1]University of Toronto Dalla Lana School of Public Health, Toronto, Ontario, Canada
[2]Centre for Vaccine Preventable Diseases, University of Toronto, Toronto, Ontario, Canada
[3]ICES, Toronto, Ontario, Canada
[4]SUNY Downstate Health Sciences University School of Public Health, Brooklyn, New York, USA
[5]Public Health Ontario, Toronto, Ontario, Canada
[6]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada
[7]Department of Family & Community Medicine, University of Toronto, Toronto, Ontario, Canada
[8]University Health Network, Toronto, Ontario, Canada
[9]Sinai Health System, Toronto, Ontario, Canada
[10]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada
[11]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada
[12]Department of Pediatrics, University of British Columbia Faculty of Medicine, Vancouver, British Columbia, Canada
[13]Vaccine Evaluation Center, BC Children's Hospital Research Institute, Vancouver, British Columbia, Canada

Acknowledgements We would like to acknowledge Public Health Ontario (PHO) for access to IPD surveillance data. Parts of this material are based on data and/or information compiled and provided by Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions and statements expressed in the material are those of the author(s) and not necessarily those of CIHI. We thank Population Data BC and BC Centre for Disease Control for acquisitive and provision of administrative data. British Columbia data were extracted, anonymised and made available to researchers by Population Data BC. Access to data provided by the data steward(s) is subject to approval but can be requested for research projects through the data steward(s) or their designated service providers. All inferences, opinions and conclusions drawn in this publication are those of the author(s) and do not reflect the opinions or policies of the data steward(s). The authors are grateful to the residents of Ontario and BC without whom this research would be impossible.

Contributors FM and SAF oversaw the study. FM, SAF, JCK, SEW, AM, SN and JW designed the study. SN and JW prepared the data and performed statistical analyses. SN drafted the manuscript. FM, SAF, JCK, SEW, SN, JW, AM and MS interpreted the results, critically reviewed and edited the manuscript and approved the final version of the manuscript. SAF is the guarantor of the study.

Funding This work was supported by the Canadian Immunization Research Network (CIRN) (Grant no. CIRN PC11). This study was also supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). SN was supported by the University of Toronto Connaught Global Challenge Award 2019-2020. JCK was supported by Clinician-Scientist Award from the University of Toronto Department of Family and Community Medicine. MS was supported via salary awards from the BC Children's Hospital Foundation and Michael Smith Health Research BC.

Disclaimer The study sponsors did not participate in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; or the decision to submit the manuscript for publication. Parts of this material are based on data and/or information compiled and provided by CIHI. However, the analyses, inferences, conclusions, opinions and

statements expressed here are solely those of the authors and do not reflect those of the funding or data sources or data steward(s); no endorsement by ICES, MOH, MLTC, PHO or CIHI is intended or should be inferred.

Competing interests 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 organisation, including vaccine manufacturers. This includes a donation from Merck to the institution that supported the salary of SAF from April 2020 to February 2023. SAF 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. MS has been an investigator on projects funded by GlaxoSmithKline, Merck, Moderna, Pfizer, Sanofi-Pasteur, Seqirus, Symvivo and VBI Vaccines. All funds have been paid to his institute, and he has not received any personal payments.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. We obtained ethics approval from the Ethics Review Boards of the Ontario Agency for Health Protection and Promotion (2019-037.01), the University of British Columbia (H19-02806) and BC Ministry of Health. This study used deidentified secondary data compiled and provided by data stewards to the researchers. As such, informed consent was not obtained by the researchers for this study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data may be obtained from a third party and are not publicly available. 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 organisations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet prespecified 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 on request, understanding that the computer programs may rely on coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

ORCID iDs
Sharifa Nasreen http://orcid.org/0000-0002-9793-113X
Shaza A Fadel http://orcid.org/0000-0002-2336-6254

REFERENCES

1 Ludwig E, Bonanni P, Rohde G, *et al*. The remaining challenges of pneumococcal disease in adults. *Eur Respir Rev* 2012;21:57–65.
2 Torres A, Blasi F, Dartois N, *et al*. Which individuals are at increased risk of pneumococcal disease and why? Impact of COPD, asthma, smoking, diabetes, and/or chronic heart disease on community-acquired pneumonia and invasive pneumococcal disease. *Thorax* 2015;70:984–9.
3 Bogaert D, De Groot R, Hermans PWM. Streptococcus pneumoniae colonisation: the key to pneumococcal disease. *Lancet Infect Dis* 2004;4:144–54.
4 Simell B, Auranen K, Käyhty H, *et al*. The fundamental link between pneumococcal carriage and disease. *Expert Rev Vaccines* 2012;11:841–55.
5 Fitzwater SP, Chandran A, Santosham M, *et al*. The worldwide impact of the seven-valent pneumococcal conjugate vaccine. *Pediatr Infect Dis J* 2012;31:501–8.
6 Davis SM, Deloria-Knoll M, Kassa HT, *et al*. Impact of pneumococcal conjugate vaccines on nasopharyngeal carriage and invasive disease among unvaccinated people: review of evidence on indirect effects. *Vaccine* 2013;32:133–45.
7 Tsaban G, Ben-Shimol S. Indirect (herd) protection, following pneumococcal conjugated vaccines introduction: a systematic review of the literature. *Vaccine* 2017;35:2882–91.
8 Shiri T, Datta S, Madan J, *et al*. Indirect effects of childhood pneumococcal conjugate vaccination on invasive pneumococcal disease: a systematic review and meta-analysis. *Lancet Glob Health* 2017;5:e51–9.
9 Luca DL, Kwong JC, Chu A, *et al*. Impact of pneumococcal vaccination on pneumonia hospitalizations and related costs in Ontario: a population-based ecological study. *Clin Infect Dis* 2018;66:541–7.
10 Nasreen S, Wang J, Kwong JC, *et al*. 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. *Vaccine* 2021;39:7545–53.
11 Nasreen S, Wang J, Sadarangani M, *et al*. Estimating population-based incidence of community-acquired pneumonia and acute otitis media in children and adults in Ontario and British Columbia using health administrative data, 2005-2018: a Canadian Immunisation Research Network (CIRN) study. *BMJ Open Respir Res* 2022;9:e001218.
12 Garcia Quesada M, Yang Y, Bennett JC, *et al*. Serotype distribution of remaining pneumococcal meningitis in the mature PCV10/13 period: findings from the PSERENADE project. *Microorganisms* 2021;9:738.
13 National Advisory Committee on Immunization (NACI). An advisory committee statement (ACS). update on the use of pneumococcal vaccines in adults 65 years of age and older – a public health perspective. 2018. Available: https://www.canada.ca/en/public-health/services/publications/healthy-living/update-on-the-use-of-pneumococcal-vaccines-in-adult.html
14 Government of Ontario. Pneumococcal conjugate 13-valent vaccine (Prevnar®13) for adults with high risk medical conditions: Q&A for health care providers. 2020. Available: https://www.health.gov.on.ca/en/public/programs/immunization/docs/pcv_hcp_qa_en.pdf [Accessed 08 Dec 2022].
15 BC Centre for Disease Control. History of immunization in BC. 2020. Available: http://www.bccdc.ca/resource-gallery/Documents/Guidelines%20and%20Forms/Guidelines%20and%20Manuals/Epid/CD%20Manual/Chapter%202%20-%20Imms/HistoryImmunization.pdf
16 Public Health Agency of Canada. Vaccine uptake in Canadian adults 2021. 2022. Available: https://www.canada.ca/content/dam/phac-aspc/documents/services/immunization-vaccines/vaccination-coverage/highlights-2020-2021-seasonal-influenza-survey/full-report/highlights-2020-2021-seasonal-influenza-survey.pdf [Accessed 11 Mar 2022].
17 Meyer BD. Natural and quasi-experiments in economics. *J Bus Econ Stat* 1995;13:151–61.
18 Linden A. Conducting interrupted time-series analysis for single- and multiple-group comparisons. *Stata J* 2015;15:480–500.
19 Canadian Institute for health information [Creator](2019): discharge abstract database (hospital separations). V2. Population data BC [publisher]. Data extract. MOH; 2019. Available: http://www.popdata.bc.ca/data
20 British Columbia Ministry of health [Creator](2019): consolidation file (MSP registration & premium billing). V2. Population data BC [publisher]. Data extract. MOH; 2019. Available: http://www.popdata.bc.ca/data
21 Appendix B: provincial case definitions for diseases of public health significance. disease: pneumococcal disease, invasive. 2019. Available: http://www.health.gov.on.ca/en/pro/programs/publichealth/oph_standards/docs/pneumococcal_cd.pdf [Accessed 20 Apr 2020].
22 BC Centre for Disease Control. Pneumococcal disease, invasive. Case definition. 2021. Available: http://www.bccdc.ca/health-professionals/clinical-resources/case-definitions/pneumococcal-disease-invasive
23 International statistical classification of diseases and related health problems, tenth revision, Canada (ICD-10-CA). 2009. Available: https://www.cihi.ca/en/submit-data-and-view-standards/codes-and-classifications
24 SAS Institute Inc. Usage NOTE 24188: modeling rates and estimating rates and rate ratios (with confidence intervals). 2015. Available: http://support.sas.com/kb/24/188.html [Accessed 12 Jun 2020].
25 Romney MG, Hull MW, Gustafson R, *et al*. Large community outbreak of streptococcus pneumoniae serotype 5 invasive infection in an impoverished, urban population. *Clin Infect Dis* 2008;47:768–74.
26 Tyrrell GJ, Lovgren M, Ibrahim Q, *et al*. Epidemic of invasive pneumococcal disease, western Canada, 2005-2009. *Emerg Infect Dis* 2012;18:733–40.
27 Ontario Agency for Health Protection and Promotion (Public Health Ontario). Immunization coverage report for school pupils in Ontario: 2017–18 school year. 2019. Available: https://www.publichealthontario.ca/-/media/Documents/I/2019/immunization-coverage-2017-18.pdf?sc_lang=en [Accessed 19 Apr 2022].
28 BC Centre for Disease Control. Immunization coverage in children by the second birthday. 2021. Available: http://www.bccdc.ca/resource-gallery/Documents/Statistics%20and%20Research/Statistics%20and%20Reports/Immunization/Coverage/2yo%20Coverage%20Birth%20Cohort.pdf [Accessed 19 Apr 2022].
29 Winje BA, Berild J, Vestrheim DF, *et al*. Efficacy and effectiveness of pneumococcal vaccination in adults – a second update of the literature. [Effekt AV Pneumokokkvaksine Hos Eldre] report 2019. Oslo Norwegian Institute of Public Health; 2022.
30 Balsells E, Guillot L, Nair H, *et al*. Serotype distribution of streptococcus pneumoniae causing invasive disease in children in the post-PCV era: a systematic review and meta-analysis. *PLoS One* 2017;12:e0177113.

31 Yahiaoui RY, Bootsma HJ, den Heijer CDJ, *et al*. Distribution of serotypes and patterns of antimicrobial resistance among commensal streptococcus pneumoniae in nine European countries. *BMC Infect Dis* 2018;18:440.
32 Ladhani SN, Collins S, Djennad A, *et al*. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000-17: a prospective national observational cohort study. *Lancet Infect Dis* 2018;18:441–51.
33 Ciruela P, Broner S, Izquierdo C, *et al*. Indirect effects of paediatric conjugate vaccines on invasive pneumococcal disease in older adults. *Int J Infect Dis* 2019;86:122–30.
34 Hanquet G, Krizova P, Valentiner-Branth P, *et al*. Effect of childhood pneumococcal conjugate vaccination on invasive disease in older adults of 10 European countries: implications for adult vaccination. *Thorax* 2019;74:473–82.
35 Løchen A, Croucher NJ, Anderson RM. Divergent serotype replacement trends and increasing diversity in pneumococcal disease in high income settings reduce the benefit of expanding vaccine valency. *Sci Rep* 2020;10:18977.
36 Dhoubhadel BG, Suzuki M, Ishifuji T, *et al*. High prevalence of multiple serotypes of pneumococci in patients with pneumonia and their associated risk factors. *Thorax* 2022;77:1121–30.
37 LeBlanc JJ, ElSherif M, Ye L, *et al*. Recalibrated estimates of non-bacteremic and bacteremic pneumococcal community acquired pneumonia in hospitalized Canadian adults from 2010 to 2017 with addition of an extended spectrum serotype-specific urine antigen detection assay. *Vaccine* 2022;40:2635–46.
38 Thorrington D, Andrews N, Stowe J, *et al*. Elucidating the impact of the pneumococcal conjugate vaccine programme on pneumonia, sepsis and otitis media hospital admissions in England using a composite control. *BMC Med* 2018;16:13.
39 Government of Canada. Vaccination coverage in Canada. 2021. Available: https://www.canada.ca/en/public-health/services/immunization-vaccines/vaccination-coverage.html#a2 [Accessed 24 Mar 2021].
40 Zeldow B, Hatfield LA. Confounding and regression adjustment in difference-in-differences studies. *Health Serv Res* 2021;56:932–41.
41 Wing C, Simon K, Bello-Gomez RA. Designing difference in difference studies: best practices for public health policy research. *Annu Rev Public Health* 2018;39:453–69.
42 Hsiao A, Hansen J, Timbol J, *et al*. Incidence and estimated vaccine effectiveness against hospitalizations for all-cause pneumonia among older US Adults who were vaccinated and not vaccinated with 13-valent pneumococcal conjugate vaccine. *JAMA Netw Open* 2022;5:e221111e221111.
43 Lewnard JA, Bruxvoort KJ, Fischer H, *et al*. Effectiveness of 13-valent pneumococcal conjugate vaccine against medically attended lower respiratory tract infection and pneumonia among older adults. *Clin Infect Dis* 2022;75:832–41.
44 Kobayashi M, Spiller MW, Wu X, *et al*. Association of pneumococcal conjugate vaccine use with hospitalized pneumonia in medicare beneficiaries 65 years or older with and without medical conditions, 2014 to 2017. *JAMA Intern Med* 2023;183:40.
45 National Advisory Committee on Immunization (NACI. Public health level recommendations on the use of pneumococcal vaccines in adults, including the use of 15-Valent and 20-Valent conjugate vaccines. 2023. Available: https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/public-health-level-recommendations-use-pneumococcal-vaccines-adults-including-use-15-valent-20-valent-conjugate-vaccines.html#sum [Accessed 24 Feb 2023].