Population Effects of Pneumococcal Conjugate Vaccines on Invasive Pneumococcal Disease in Canada — A Targeted Literature Review

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Background

- Routine childhood immunization with pneumococcal conjugate vaccines (PCVs) has been widely used worldwide to reduce the incidence of invasive pneumococcal disease (IPD)
- In Canada, the National Advisory Committee on Immunization (NACI) recommended the 7-valent PCV (PCV7) with three infant doses and one booster (3+1) for children <2 years in 2002; the vaccine was introduced in different provinces between 2002 and 2006 with varying dosing schedules (3+1 or 2+1)[1,2]
- In 2009, NACI recommended the 10-valent PCV (PCV10) 3+1 schedule, which was replaced by the 13-valent PCV (PCV13) 3+1 in 2010[3,4]
- PCV13 was initiated across provinces from 2010 to 2011, mostly in 2+1 schedule; some implemented PCV10 briefly before transitioning to PCV13[3,4]
- Understanding the population-level effects of these lower-valent PCVs may inform vaccine policy for newer higher-valent PCVs (such as PCV15 and PCV20), which have been recently introduced in Canada

Objective

- To synthesize the evidence on the population-level effects of PCVs on IPD incidence in Canada based on a targeted review of recent literature

Methods

- A targeted literature review was conducted in MEDLINE and Embase on February 19, 2025 to identify studies on population-level effects of PCVs published since January 2016, the end date of prior systematic reviews[5]
- Studies were selected using the following PICOS criteria:
  - **Population:** Any population in Canada, excluding studies limited to vaccinated children only
  - **Intervention:** Any PCV, including PCV7, PCV10, PCV13, PCV15, PCV20
  - **Comparator:** Any of the listed interventions or no comparator
  - **Outcomes:** Incidence rates (IRs) of IPD (overall, vaccine-type [VT], and non-vaccine-type [NVT]) reported before and after a PCV introduction
  - **Study design:** Population-based or laboratory-based surveillance studies; observational studies (cohort, case-control, cross-sectional)
  - **Other criteria:** Full-text journal articles in English; studies conducted in Canada or multi-country studies reporting Canada-specific data separately
- **Data extraction**
  - Study characteristics (author, year, study population, PCV investigated, study type, geographic region, and age groups) were extracted from included studies
  - **Outcomes**
    - IPD IRs, including overall, VT-IPD, and NVT-IPD, were extracted for periods before and after PCV introduction. Two types of IRs were extracted: period and annual IRs
      - Period IRs referred to IRs reported for pre- and post-PCV periods defined in each study
      - Annual IRs referred to IRs reported for individual years before and after PCV introduction. Only annual IRs for the last year before and the last year after PCV introduction were extracted
    - Percentage changes in IRs before and after a PCV introduction were extracted directly from the included studies or calculated based on extracted IRs
- **Data analysis and synthesis**
  - Percentage changes in IPD IRs before and after each PCV introduction were summarized by serotype category and age group and reported as medians and interquartile ranges
    - If a study reported both period IRs and annual IRs, the IRs used in the main analyses of that study were used
  - Subgroup analyses by geographic region were conducted
  - Evidence of herd protection was summarized based on percentage changes in VT-IPD IRs; evidence of serotype replacement was summarized based on percentage changes in NVT-IPD IRs
  - Temporal trends before and after each PCV introduction were also evaluated, if reported, to supplement the evidence based on percentage changes in IRs

Results

Overview of identified studies

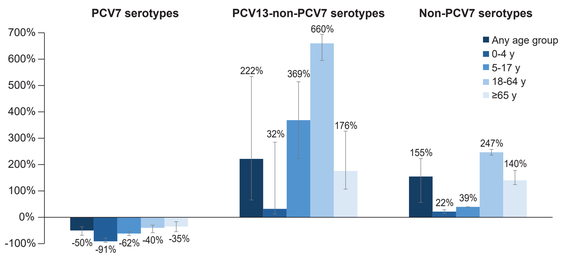
- A total of 11 studies were included in this review
  - Most studies included all ages; only one included adults only
  - Five investigated both PCV7 and PCV13, 5 focused on PCV13 only, and 1 investigated PCV7 and PCV10/13
  - All studies used surveillance data and identified IPD cases based on laboratory testing
  - Two studies used national data; the rest were regional studies (Ontario [ON] 4, British Columbia [BC] 3, Alberta [AB] 2, Manitoba [MB] 1, and Quebec [QC] 1)
  - Ten reported overall IPD IRs, 6 reported IRs for PCV7 IPD, 7 for PCV13-non-PCV7 IPD, 8 for PCV13 IPD, 2 for non-PCV7 IPD, and 8 for non-PCV13 IPD
  - Six studies reported annual IRs only; 1 reported period IRs only; 4 reported both

Percentage changes in IRs

Serotype-specific IPD

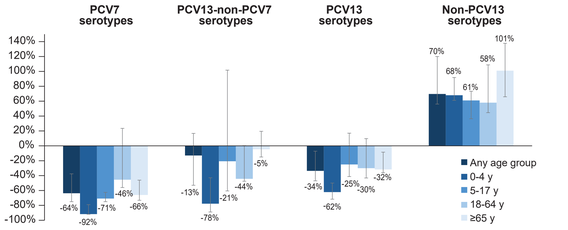
- PCV7 period vs pre-PCV period (**Figure 1**)
  - PCV7 IPD IRs declined following PCV7 introduction (median: −35% to −91% across age groups), with the greatest reduction in children <5 years
  - Non-PCV7 IPD IRs increased substantially in the PCV7 period (median: 22% to 247% across age groups), with the largest increase in adults 18–64 years (247%), followed by adults ≥65 years (140%)
  - PCV13-non-PCV7 IPD IRs showed larger percentage increases in the PCV7 period (median: 32% to 660% across age groups), compared to non-PCV7 IPD IRs
- PCV13 period vs PCV7 period (**Figure 2**)
  - PCV7 IPD IRs continued to decline following PCV13 introduction (median: −46% to −92% across age groups), though substantial variability was observed in adults 18–64 years across studies, ranging from reductions to increases
  - Changes in PCV13-non-PCV7 IPD IRs varied across age groups: large and consistent reductions were observed in children <5 years (median: −78%), while substantial variability was observed across studies in other age groups
  - PCV13 IPD IRs showed overall reductions after PCV13 (median: −25% to −62% across age groups); changes varied considerably across studies in older age groups (≥5 years)
  - Non-PCV13 IPD IRs increased across age groups, with median increase ranging from 58% in adults 18–64 years to 101% in adults ≥65 years

Figure 1. Changes in VT-IPD and NVT-IPD incidence in PCV7 vs pre-PCV period



IPD, invasive pneumococcal disease; IQR, interquartile range; NVT, non-vaccine type; PCV, pneumococcal conjugate vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; VT, vaccine type.
Notes: Population-level effects were estimated as relative change in incidence before and after PCV7 introduction.
Median percentage change and interquartile ranges (IQRs) are shown.

Figure 2. Changes in VT-IPD and NVT-IPD incidence in PCV13 vs PCV7 period

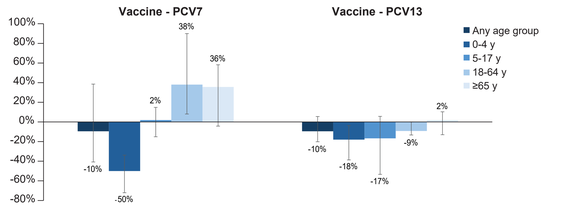


IPD, invasive pneumococcal disease; IQR, interquartile range; NVT, non-vaccine type; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; VT, vaccine type.
Notes: Population-level effects were estimated as relative change in incidence before and after PCV13 introduction.
Median percentage change and interquartile ranges (IQRs) are shown.

Overall IPD (Figure 3)

- Overall IPD IRs declined among children <5 years following PCV7 introduction (median: −50%), while remaining stable or increasing in older age groups (median: 2% to 38%)
- Overall IPD IRs showed modest median reductions following PCV13 introduction in the age groups <65 years (−9% to −18%), while remaining stable in adults ≥65 years (median: 2%)
- Changes in overall IPD IRs varied substantially across studies in each age group

Figure 3. Population effects of PCV7 and PCV13 on overall IPD incidence



IPD, invasive pneumococcal disease; IQR, interquartile range; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.
Notes: Population-level effects were estimated as relative change in incidence before and after PCV7 (left) and PCV13 (right) introduction.
Median percentage change and interquartile ranges (IQRs) are shown.

Percentage changes in IRs by geographic region

- PCV7 vs pre-PCV period (**Table 1A**)
  - Reductions in PCV7 IPD IRs and increases in non-PCV7 IPD IRs were observed across age groups at the national and regional levels
  - Consistent reductions in overall IPD IRs were observed among children <5 years across regions, while changes varied substantially across regions in older age groups
- PCV13 vs PCV7 period (**Table 1B**)
  - PCV7 IPD IR reduced in almost all age groups and regions but not at the national level
  - PCV13-non-PCV7 IPD IRs declined consistently across age groups at the national level but varied across age groups and regions
  - Reductions in PCV13 IPD IRs were observed across age groups at the national and regional levels, except children 5–17 years
  - Non-PCV13 IPD IRs increased in almost all age groups at the national and regional levels
  - Changes in overall IPD IRs varied substantially across regions in each age group

Table 1. Population-level effects of PCV7 and PCV13 by geographic region

Table 1A. PCV7 vs pre-PCV period

Serotypes	Age group (years)	National	Regional[a]
PCV7	0–5	−99%	−78%
	5–17	−77%[b]	−46%
	18–64	−77%[b]	−30%
	≥65	−77%[b]	−23%
	0–100	−65%	−53%
PCV13-non-PCV7	0–5	538%	12%
	5–17	660%	77%
	18–64	660%	630%
	≥65	660%	136%
	0–100	533%	227%
Non-PCV7	0–5	—	22%
	5–17	—	39%
	18–64	—	247%
	≥65	—	140%
	0–100	403%	169%
Overall IPD	0–5	—	−64% to −43%
	5–17	—	−32% to 13%
	18–64	—	−5% to 171%
	≥65	—	−15% to 83%
	0–100	—	−5% to 60%

Table 1B. PCV13 vs PCV7 period

Serotypes	Age group (years)	National	Regional[a]
PCV7	0–5	—	−97% to −79%
	5–17	—	−75% to −63%
	18–64	—	−48% to 7%
	≥65	—	−97% to −60%
	0–100	60%	−50% to −15%
PCV13-non-PCV7	0–5	−89%	−90% to −32%
	5–17	−60%	−100% to 178%
	18–64	−48%	−63% to 57%
	≥65	−58%	−24% to 8%
	0–100	−53%	1% to 16%
PCV13	0–5	—	−90% to −37%
	5–17	—	−99% to 58%
	18–64	—	−59% to −5%
	≥65	—	−41% to −28%
	0–100	−33%	−27% to −5%
Non-PCV13	0–5	70%	−10% to 84%
	5–17	46%	−99% to 111%
	18–64	56%	41% to 95%
	≥65	74%	38% to 115%
	0–100	118%	97% to 119%
Overall IPD	0–5	—	−40% to 25%
	5–17	—	−100% to 30%
	18–64	—	−11% to −4%
	≥65	—	−4% to 10%
	0–100	—	−34% to −2%

AB, Alberta; BC, British Columbia; IPD, invasive pneumococcal disease; MB, Manitoba; ON, Ontario; PCV, pneumococcal conjugate vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; QC, Quebec.

Trend in IRs

- PCV7 period
  - PCV7 IPD IRs showed a consistent declining trend in the overall population across studies; however, fluctuations were observed across different age groups
  - Non-PCV7 IPD IRs exhibited an upward trend throughout the PCV7 period at the national and regional levels
    - The only exception was BC, where an outbreak involving a non-PCV7 serotype occurred in the middle of the PCV7 period; thus non-PCV7 IPD IRs increased first and then decreased during the PCV7 period
  - Overall IPD IRs did not show a consistent trend across age groups and regions
    - Outbreaks involving non-PCV7 serotypes in adults substantially increased the overall IPD IRs in the PCV7 period in BC and AB
- PCV13 period
  - While PCV7 IPD IRs decreased substantially during the PCV13 period, studies using recent data showed an upward trend in PCV7 IPD IRs after 2014 (absolute IR increase: 0.4 to 1.7 per 100,000 person-years; percentage increase: 65% to 400%)
  - PCV13-non-PCV7 IPD IRs and PCV13 IRs showed consistent declining trends in the overall population across studies; however, such trends varied across age groups
  - Non-PCV13 IPD IRs showed an increasing trend in the overall population and all age groups in most studies
    - In MB, an outbreak involving a non-PCV13 serotype occurred in 2010, the year when PCV13 was introduced, and thus led to an overall decreasing trend in non-PCV13 IPD IR
  - Overall IPD IRs were generally stable during the PCV13 period in the overall population but varied across age groups and time periods
    - Overall IPD IRs fluctuated within each age group without a consistent pattern
    - Data before 2014 showed flat or decreasing trends in the overall population, while an upward trend was observed at both national and regional levels based on data after 2014

Summary of findings

- PCV7 effects
  - Reductions in PCV7 IPD IRs support direct effects in young children and herd protection effects across all age groups
  - Increases in non-PCV7 IPD IRs support serotype replacement effects across all age groups
  - Overall IPD IRs decreased in children <5 years but increased in adults ≥18 years in the PCV7 period
- PCV13 effects
  - Reductions in PCV7 IPD IRs support direct effects in young children and herd protection effects across all age groups, though PCV7 IPD IRs showed an upward trend in the overall population starting in 2014
  - Findings for PCV13-non-PCV7 IPD IRs were mixed across age groups
    - Reductions in PCV13-non-PCV7 IPD IRs support direct effects and herd protection in young children
    - However, there was substantial variability across studies in older age groups (≥5 years), ranging from significant reductions to significant increases
    - Consistent declining trends across studies support herd protection effects in the overall population; however, trends varied across age groups
  - Increases in non-PCV13 IPD IRs support serotype replacement effects across all age groups
  - Overall IPD IRs did not show consistent trends across age groups and regions following PCV13 introduction
- While age-specific and regional data are informative, these results should be interpreted with caution as small numbers of cases may lead to substantial year-to-year fluctuations in IRs

Limitations of existing studies

- Surveillance type
  - Many studies were based on passive surveillance systems, which may have led to variations in case reporting across years
- Fluctuations in IPD IRs
  - Outbreaks caused a sudden increase in IPD IRs, which affected the evaluation of PCV effects
  - Small sample sizes led to fluctuations in IPD IRs, making it challenging to detect underlying trends using observed data
- Annual vs period incidence
  - Due to the fluctuations in IRs, estimates of PCV effects were affected by the choice of annual vs period IRs and the time frame during which IRs were assessed
  - Using period incidence could mask the changes before and after PCV introduction if IRs had the opposite trends between the two periods
  - Using annual incidence based only on the last year before and after PCV introduction ignores year-to-year fluctuations, which may lead to erroneous conclusions
  - The mean differences in percentage change in IRs based on annual vs period IRs ranged from −42% to 87% across serotype categories; in some cases, using annual vs period IRs led to different conclusions
- Given these limitations, both percentage changes in IRs and temporal trends should be considered when evaluating the effects of PCVs
- In addition to observed data, time series analyses adjusting for underlying trends and outbreaks are warranted to better characterize the true effects of PCVs
- Improved surveillance systems and standardized data collection would enhance the accuracy and comparability of future studies

Conclusions

- The incidence of VT-IPD declined after PCV7 and PCV13 introduction across age groups at the national level in Canada, consistent with both direct and herd protection effects
- Changes in the incidence of PCV13-non-PCV7 IPD varied considerably by region in older age groups (≥5 years)
- The incidence of NVT-IPD increased following PCV introductions at the national and regional levels, suggesting widespread serotype replacement
- Overall IPD IRs did not show consistent trends across age groups and regions
- The effects of PCVs should be assessed comprehensively based on both relative changes in incidence and temporal trends

References

1. McClure CA, et al. *Can J Infect Dis Med Microbiol.* 2006;17(1):19-26.
2. Kellner J. *Paediatr Child Health.* 2011;16(4):233-40.
3. Dion SB, et al. *Vaccine.* 2021;39(22):3007–3017.
4. Wilson MR, et al. *Infect Dis Ther.* 2020;9:341–353.
5. Tsaban G, et al. *Vaccine.* 2017;35(22):2882-2891.

Disclosures

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