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ORIGINAL RESEARCH

Historical Population-Level Impact of Infant 13-Valent Pneumococcal Conjugate Vaccine (PCV13) National Immunization Programs on Invasive Pneumococcal Disease in Australia, Canada, England and Wales, Israel, and the United States

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ABSTRACT

Introduction: This study estimates the annual population-level impact of 13-valent pneumococcal conjugate vaccine (PCV13) infant national immunization programs (NIPs) on vaccine-type and non-vaccine type invasive pneumococcal disease (IPD) incidence across all ages using national surveillance data.

Methods: We identified countries (Australia, Canada, England and Wales, Israel, and the US) with national IPD active surveillance data that introduced the seven-valent PCV (PCV7) followed by PCV13, which also reported annual serotype- and age group-specific incidence. We extracted IPD incidence by serotype groupings [PCV13 minus PCV7 (PCV13-7) serotypes; PCV13-7 serotypes excluding serotype 3; non-PCV13 serotypes; and the 20-valent (PCV20) minus PCV13 (PCV20-13) serotypes] and by age groups (< 2 years, 2–4 years, 5–17 years, 18–34 years, 35–49 years, 50–64 years, and ≥ 65 years). For each country, we calculated the annual relative change in IPD incidence (percent change), and the corresponding incidence rate ratio (IRR), for 7 years post introduction compared to the year prior to PCV13 program initiation.

Results: PCV13-7 vaccine-type IPD incidence consistently decreased over time following introduction of PCV13 across countries, reaching an approximate steady state after 3–4 years in ages < 5 years, with roughly 60–90% decrease (IRRs = 0.1–0.4) and after 4–5 years in ages ≥ 65 years with approximately 60–80% decrease (IRRs = 0.2–0.4). Incidence declines were more substantial for the PCV13-7 grouping when excluding serotype 3. Non-PCV13 serotype incidence was variable by country and age group, ranging from virtually no serotype replacement compared to the PCV7 period across ages in the US to increases for other countries ranging from 10 to 204% (IRRs = 1.10–3.04) in children < 5 years and 41% to 123% (IRRs = 1.41–2.23) in ages ≥ 65 years.

Conclusions: Countries with longstanding PCV13 infant NIPs have observed substantial direct and indirect benefits, which are demonstrated in this study by the reduction in PCV13-7 IPD incidence compared to PCV7 period in all

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age groups. Over time, non-PCV13 serotypes have emerged in response to the reduction of incidence of PCV13-unique serotypes. Higher-valent PCVs are needed to address this emerging pneumococcal disease burden as well as the direct vaccination of both pediatric and adult populations against the most prevalent circulating serotypes.

Keywords: Pneumococcal disease; Indirect effects; Pneumococcal vaccination; Public health impact; PCV13; PCV20; Retrospective analysis; Vaccine impact; Serotype replacement

Key Summary Points

Why carry out this study?

As novel pneumococcal conjugate vaccines (PCV) with greater serotype coverage are introduced into infant national immunization programs (NIP), it will be important to understand the current epidemiologic trends for these serotypes as well as for currently covered serotypes.

The objective of this study was to estimate the annual population-level impact of PCV13 NIPs on vaccine-type and non-vaccine type (NVT) invasive pneumococcal disease (IPD) incidence among children and adults using national surveillance data of countries that switched from PCV7 to PCV13 in their NIP.

What was learned from this study?

Infant PCV13 vaccination with high population-level uptake rates has led to substantial reductions in vaccine-type IPD in the first 7 years across all age groups following introduction in countries where the vaccine was introduced (i.e., both direct and indirect protection was observed). Conversely, an increase in NVT IPD was observed across all age groups.

The impact of PCV13 was more substantial in ages < 5 years compared with ages ≥ 65 years, illustrating the need for an adult PCV program covering many of the same serotypes as the pediatric PCV program rather than relying on pediatric herd effects exclusively. Despite similarities in vaccine-type IPD reductions, the NVT IPD trends were variable, which may have been affected by schedule, uptake, age, genetics and environment, geographic setting, and quality of surveillance, among others.

INTRODUCTION

Pneumococcal disease is caused by 101 different pneumococcal serotypes, but most cases are caused by a subset of serotypes [13, 28]. Since the early 2000s, pneumococcal conjugate vaccines (PCVs) have been available as part of pediatric national immunization programs (NIPs) for prevention of pneumococcal disease. PCVs provide direct protection against invasive pneumococcal disease (IPD) in vaccinated infants, but also provide indirect effects by reducing nasopharyngeal carriage and transmission of vaccine-type serotypes, which correspond to decreases in IPD incidence in unvaccinated populations [37].

After the introduction of the 7-valent (PCV7) globally into NIPs, a dramatic reduction in pneumococcal disease related to PCV7 serotypes was observed in vaccinated children in countries with high vaccine uptake [7, 36]. Countries with PCV7 infant NIPs observed indirect effects in unvaccinated populations due to decreased PCV7 serotype carriage and transmission by vaccinated children [37].

After the success of PCV7 introduction, a subsequent increase in non-vaccine serotype incidence occurred in many countries, most commonly attributed to serotypes 19A, 7F, and 1 [36]. In 2009, a 13-valent vaccine (PCV13) was introduced, continuing coverage of PCV7 serotypes and adding six unique, non-vaccine serotypes to the formulation (1, 3, 5, 6A, 7F, and

19A). A rapid reduction in PCV13-unique serotype disease was observed in all ages after implementation of PCV13 in pediatric NIPs globally [17], coupled with maintained suppression of PCV7 serotype disease. However, some PCV13 countries have also observed a rise in incidence of non-PCV13 serotypes, similar to the replacement of non-vaccine serotypes observed post-PCV7 implementation [41]. Multiple countries with sustained use of PCV13 in pediatric NIPs observed an increase in non-PCV13 serotype incidence, including but not limited to serotypes 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 22F, 23B, 24F, 33F, 35B, and 38 [19, 22–24].

The objective of this study was to estimate the annual population-level impact of PCV13 NIPs on vaccine-type and non-vaccine type (NVT) IPD incidence among children and adults using national surveillance data of countries that switched from PCV7 to PCV13 in their NIP. A 20-valent vaccine (PCV20), which covers seven additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) beyond PCV13, is in advanced clinical development for pediatric populations and has been licensed in adults [10–12, 27, 31]. As of February 2023, it has been recommended and publicly reimbursed for adults in Canada, Denmark, Greece, Israel, Spain, Sweden, and the USA. Given that previous studies have estimated the current clinical and economic burden of disease associated with these serotypes [40], evaluating historical incidence trends of vaccine- and non-vaccine-serotype incidence across countries may help to inform expected patterns, rates of reduction, and time to stabilization of vaccine-type and NVT IPD incidence.

METHODS

Invasive Pneumococcal Disease Data

We identified countries that introduced PCV7 followed by PCV13 in the pediatric NIP, with national IPD surveillance data that report annual serotype- and age group-specific incidence in both PCV periods. Australia, Canada, England and Wales, Israel, and the US met these criteria. We extracted annual incidence by serotype and age group from available active surveillance systems (Table 1) [3, 6, 8, 14, 21, 39]. For Israel and the US, reported incidence rates for ages 0 to < 5 years were applied equally to ages 0 to < 2 and 2–-4 years. For Israel, Canada, and England and Wales, reported incidence rates for 18–49 years of age were applied equally to ages 18–34 and 35–49 years. Because PCV13 was introduced in Israel in November 2010 and in England and Wales in April 2010, the pre-PCV13 year was assumed to be 2009/2010 for both, given these countries report epidemiologic data from July to June each year. Analyses were capped 7 years after PCV13 introduction because all countries contributed data for the entire 7 year period. Although all countries used PCV7 followed by PCV13 in their NIP, NIPs varied by PCV uptake, schedule (3 + 1, 2 + 1, and 3 + 0 schedules), PCV10 regional use (e.g., Quebec in Canada), availability of an adult vaccination program (PCV13 or PPV23), and PCV13 infant supplemental dose catch-up programs. Data sources, PCV pediatric NIP schedules and years of NIP implementation, and adult PCV recommendations are summarized in Table 1. In each of these countries the estimated vaccination uptake was high (Table S1 of the Supplementary Material). Throughout the analyses, the observed changes in incidence among vaccinated age groups aged < 5 years, including routine and catch-up vaccination, were considered as both direct and indirect vaccine effects. For simplicity, in ages ≥ 5 years, we considered the observed changes in incidence as indirect vaccine effects, as the proportion of individuals within this age group vaccinated with PCV13 within the time period is very small. This study is based on previously conducted studies or collected data and does not contain any new studies with human participants or animals.

Analyses

Individual Country Analysis

For each country, we calculated the annual relative change in IPD incidence and the corresponding incidence rate ratio (IRR) compared to

Table 1 Countries included and data sources

Country	Data source	PCV pediatric NIP schedule and years of included data	NIP with reimbursement for adults ≥ 65 (during the years of included data)
Australia	NNDSS [2, 26][a]	2011: PCV7, 3 + 0 2012–2018: PCV13, 3 + 0/2 + 1[b] Catch-up: one additional dose for all children ages aged 12–35 months	PPV23 only
Canada	Public Health Agency of Canada [14, 15][c]	2010: PCV7, 2 + 1 2011–2017: PCV13, 2 + 1[d] Catch-up in two provinces (Ontario and Manitoba): one additional dose for all children ages aged 12–35 months	PPV23 only
England and Wales	Public Health England [21][c]	2009/10: PCV7, 2 + 1 2011–2017: PCV13, 2 + 1[e] No catch-up	PPV23 only
Israel	Israeli Pediatric Bacteremia and Meningitis Group Network [6, 39][c,f]	2009/10: PCV7, 2 + 1 2011–2017: PCV13, 2 + 1 [g] No catch-up	PPV23 only
United States	ABC Data [8][f]	2009: PCV7, 3 + 1 2010–2016: PCV13, 3 + 1 Catch-up: one additional dose for all children ages 14–59 months	Only PPV23 until 2014; both PCV13 and PPV23 from 2014–2016

ABC Active Bacterial Core; *CDC* Centers for Disease Control and Prevention; *NNDSS* National Notifiable Disease Surveillance System

[a]Cases for 2009–2019 by age were obtained from the Australian Government Department of Health (Australian Government Department of Health, 2020). Serotype-specific IPD cases were not reported for two regions in Australia: Australian Capital Territory (ACT) was not included at all, and Western Australia (WA) does not report the data by serotype. Cases for WA for 2017–2019 were obtained through direct correspondence with the WA Department of Health. Incidence was estimated using Australian population estimates [1]. We assumed incidence for 5–19 is applicable for 5–17 year olds and 20–34 is applicable for 18–34 year olds

[b]Australia implemented a 3 + 0 schedule and transitioned to a 2 + 1 schedule in 2018. PCV13 was introduced in July 2011, so we assumed 2011 calendar year was pre-PCV13 year and 2012 was year 1 of PCV13

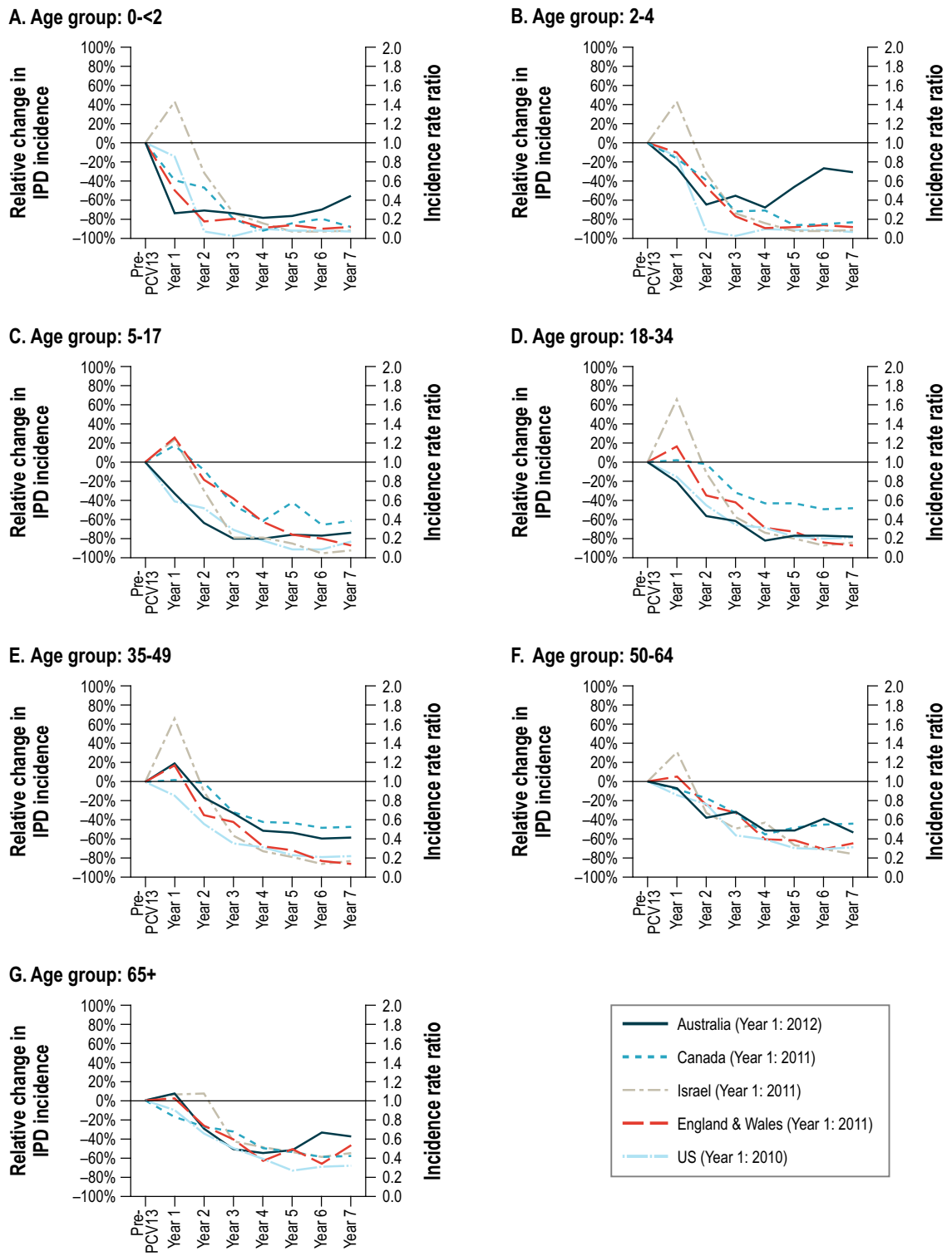
[c]As IPD data were provided for those 18–49 years of age, the same incidence was assumed for among 18–34 and 35–49 year olds

[d]PCV10 (Synflorix) replaced PCV7 as the vaccine of choice in 2009 in four provinces briefly until 2011

[e]PCV13 was introduced in England and Wales in April 2010; thus, pre-PCV13 year was assumed to be 2009/2010. The UK switched from 2 + 1 to 1 + 1 schedule as of January 2020. All data for England and Wales presented in this article were during the period when the UK had a 2 + 1 schedule

[f]The same incidence was assumed for among 0 to < 2 and 2–4 as IPD counts were provided for 0 to < 5 year olds

[g]PCV13 was introduced in November 2010; thus, pre-PCV13 year was assumed to be 2009/2010. Case counts for $\geq$ 18 year olds were not reported in 2008


A. Age group: 0-<2
B. Age group: 2-4
C. Age group: 5-17
D. Age group: 18-34
E. Age group: 35-49
F. Age group: 50-64
G. Age group: 65+
Relative change in IPD incidence
Incidence rate ratio
100%
80%
60%
40%
20%
0%
−20%
−40%
−60%
−80%
−100%
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Pre-PCV13
Year 1
Year 2
Year 3
Year 4
Year 5
Year 6
Year 7
Australia (Year 1: 2012)
Canada (Year 1: 2011)
Israel (Year 1: 2011)
England & Wales (Year 1: 2011)
US (Year 1: 2010)

◀**Fig. 1** PCV13- PCV7 serotypes (serotypes 1, 5, 7F, 3, 6A, 19A). *PCV* pneumococcal conjugate vaccine; *UK* England and Wales; *US* United States. PCV7 is the 7-valent PCV; PCV13 is the 13-valent PCV. Incidence rate ratios calculated as $Incidence_x/Incidence_0$, where x represents the years since PCV13 was introduced and 0 represents the year prior to PCV13 introduction. The figures present the percentage incidence change and incidence rate ratios for age groups < 2 (**A**), 2–4 (**B**), 5–17 (**C**), 18–34 (**D**), 35–49 (**E**), 50–64 (**F**), and ≥ 65 (**G**)

the incidence in the year prior to introduction of a PCV13 program. Specifically, we estimated the relative change in incidence and IRR for seven age groups (< 2 years; 2–4 years; 5–-17 years; 18–34 years; 35–49 years; 50–64 years; ≥ 65 years) and four serotype groups (PCV13 minus PCV7 serotypes [PCV13-7], namely 1, 3, 5, 6A, 7F, and 19A; PCV13-7 serotypes excluding serotype 3 [PCV13-7-3]; non-PCV13 serotypes [NVT]; and serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F, which are covered in PCV20 currently under development for pediatric use [PCV20-13]). For the comparator year, we included 1 year of PCV7 data for each country, which was 2011 for Australia, 2010 for Canada, 2010 for Israel, 2010 for England and Wales, and 2009 for the US. Specifically, we included data as follows: for Australia, data from 2012 to 2018; for Canada, 2011 to 2017; for Israel, 2011 to 2017; for England and Wales, 2011 to 2017; for the US, 2010 to 2016. For consistency, we included only the first 7 years following PCV13 introduction so as not to exclude any countries for any years. The annual relative incidence change for each year was estimated as $(Incidence_x–Incidence_0)/Incidence_0$, where the subscripts represent the years of PCV13 coverage (i.e., year 0 is the year prior to PCV13 introduction and year x is the number of years PCV13 has been implemented in the NIP). Similarly, the IRR was calculated as $Incidence_x/Incidence_0$.

Combined Country Analysis

For the vaccine-type serotype groupings, the average annual relative change in IPD incidence and corresponding IRR across all countries for each age group were calculated. The average annual relative change for non-vaccine serotypes was not estimated because of substantial variability in trends across countries and age groups.

RESULTS

PCV13 Serotype Results

Individual Country Analysis Results

PCV13-7 serotype IPD incidence decreased rapidly and substantially in each country compared to rates in the year prior to PCV13

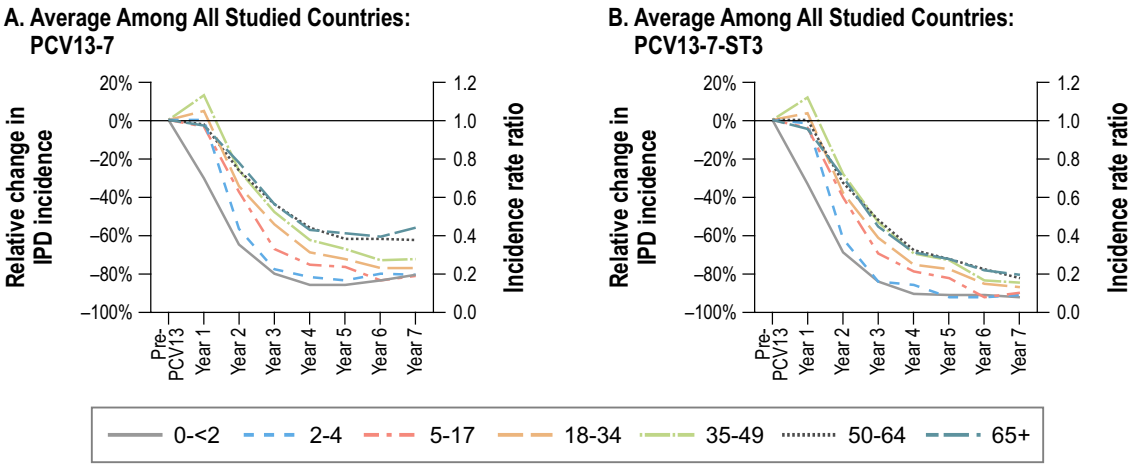
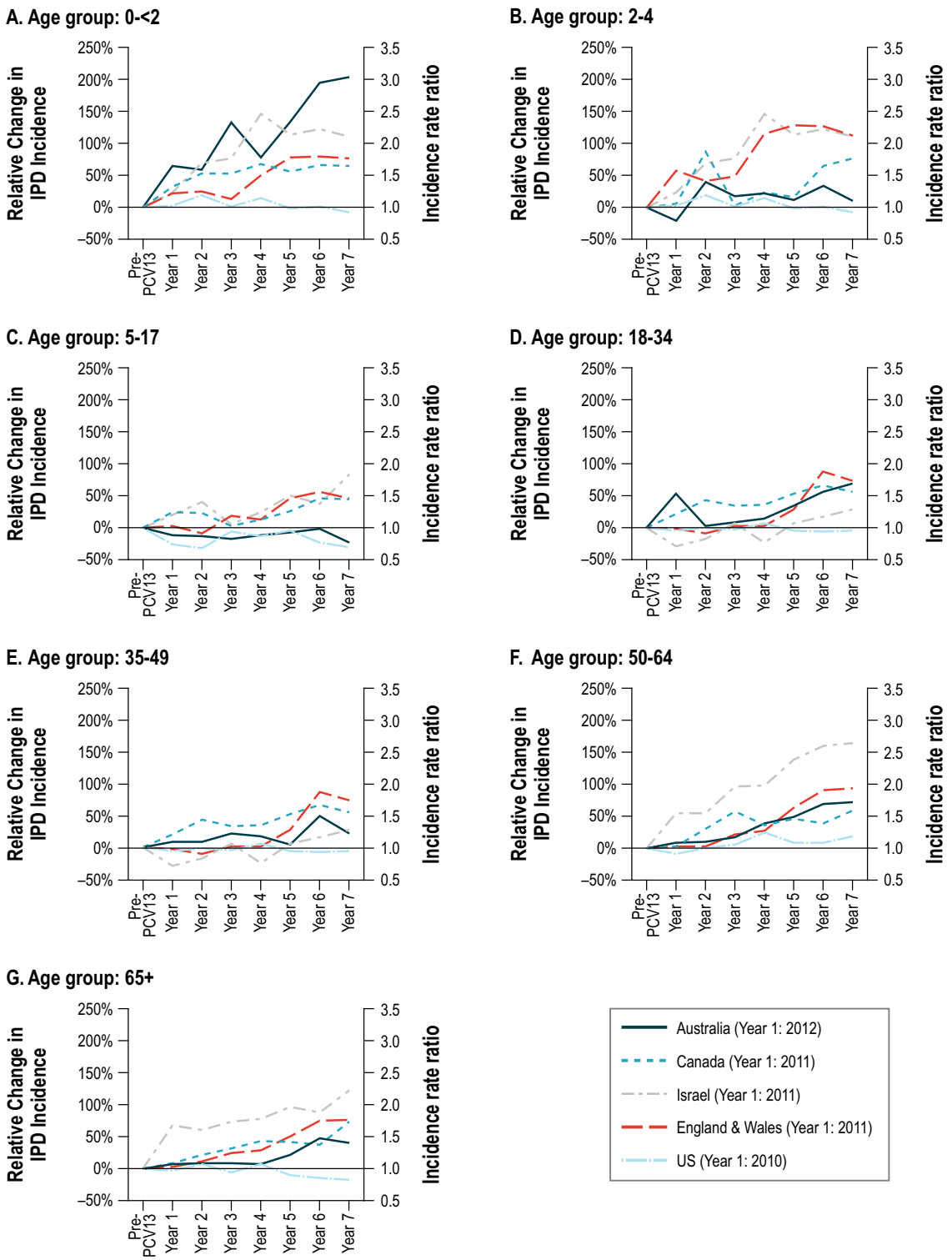


Fig. 2 Average age-specific PCV13-7 incidence reduction among studied countries. PCV13-7 = serotypes unique to PCV13 compared to PCV7. PCV = pneumococcal conjugate vaccine


A. Age group: 0-<2
B. Age group: 2-4
C. Age group: 5-17
D. Age group: 18-34
E. Age group: 35-49
F. Age group: 50-64
G. Age group: 65+
Relative Change in IPD Incidence
Incidence rate ratio
250%
200%
150%
100%
50%
0%
−50%
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Pre-PCV13
Year 1
Year 2
Year 3
Year 4
Year 5
Year 6
Year 7
Australia (Year 1: 2012)
Canada (Year 1: 2011)
Israel (Year 1: 2011)
England & Wales (Year 1: 2011)
US (Year 1: 2010)

◀**Fig. 3** Non-vaccine type serotypes. PCV = pneumococcal conjugate vaccine; UK = England and Wales; US = United States. PCV7 is the 7-valent PCV; PCV13 is the 13-valent PCV. Incidence rate ratios calculated as $Incidence_x/Incidence_0$, where x represents the years since PCV13 was introduced and 0 represents the year prior to PCV13 introduction. The figures present the percentage incidence change and incidence rate ratios for age groups < 2 (**A**), 2–4 (**B**), 5–17 (**C**), 18–34 (**D**), 35–49 (**E**), 50–64 (**F**) and ≥ 65 (**G**)

introduction (Fig. 1). Rates of decline and time to stabilization of IRRs (i.e., steady state) were generally consistent across countries but varied by age group. Among children < 5 years, steady state appears to be reached in year 3 or 4 of PCV13 use. Among children 5–17 years and adults, disease reduction appears to stabilize at year 4 or 5 after introduction of PCV13 in the pediatric NIP. For most countries and across all age groups, disease trends remained relatively stable from year 5 onwards. Decreases in PCV13-7 serotype IPD incidence in each age group were generally consistent across the five countries following the introduction of PCV13 in the pediatric NIP. Reductions in IPD incidence among children < 5 years stabilized at an 84–93% reduction in incidence (IRR = 0.07–0.16) in year 4 of the program, except in Australia, which observed a rise in disease after reaching 78% protection (IRR = 0.22) in year 4 of the program. For ages ≥ 65 years, PCV13-7 IPD reduction plateaued at 47–69% (IRR = 0.31–0.53) in year 5 of the program. Finally, IPD incidence attributable to PCV13-7 serotypes decreased more rapidly among children than adults in the first years following the introduction of PCV13 in the infant NIP.

Sensitivity analyses of PCV13-7 serotypes excluding serotype 3 (PCV13-7–3) are included in Supplementary Material (Fig S1a-S1g). IRR country ranges were slightly lower compared with IRR country ranges including serotype 3 (Fig. 1a–g). The difference was most apparent in Australia in those 2–4 years and for ages ≥ 50 years. For ages < 5 years, excluding serotype 3 resulted in an IRR that ranged by country from 0.06 to 0.24 in year 4 of the program. For ages ≥ 65 years, IRR without serotype 3 ranged by country from 0.12 to 0.41 in year 5 of the program.

Combined Country Analysis Results

When incidences of PCV13-7 serotypes were pooled across the five countries, an 81% average reduction in IPD caused by PCV13-7 serotypes (IRR = 0.19) among 0 – < 2 year age group was observed in year 4 of pediatric PCV13 use (Fig. 2a). Decreases were more substantial among younger vaccinated age groups (direct effect) than older age groups (primarily indirect effect). When excluding serotype 3 from the vaccine-type grouping (Fig. 2b), the decline was ≥ 80% by year 7 for all age groups, whereas the decline when including serotype 3 ranged from 59–80% across age groups.

Non-Vaccine Serotype Results

Incidence of NVT IPD generally increased compared to rates in the year prior to PCV13 introduction except for the US in all age groups (Figs. 3a–g). Trends across the other four countries and age groups were heterogeneous. The increase in NVT IPD incidence was more pronounced among children < 2, 50–64, and ≥ 65 years compared to other age groups. Relative changes in NVT IPD were observed following the introduction of PCV13 in the NIP for ages < 2 after 7 years, ranging from an 8% decrease in the US (IRR = 0.92) to a 204% increase in Australia (IRR = 3.04). The US and Australia observed little to no increase in NVT IPD incidence among children ages 2–4 years and 5–17 years by year 7 of the program, whereas England and Wales, Israel, and Canada observed relative increases of 77–111% (IRR = 1.77 to 2.11) and 45–83% (IRR = 1.45 to 1.83), respectively. By year 7 of the PCV13 program, for age group 50–64 years, all countries except for the US observed a substantial rise in NVT IPD ranging from 60 to 164% (IRR = 1.60 to 2.64) relative to the PCV7 period. In those ≥ 65 years, the US observed a slight decrease in NVT disease, while other countries observed increases between 41 and 123% (IRR = 1.41 and 2.23) in year 7.

Individual country graphs for PCV20-13 serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) are presented in the Supplementary Material (Fig S2a-S2g). Increases in incidence by serotype group were variable across countries, ranging from little to no increase for the US across all age groups (year 7) to a 623% increase (IRR = 7.23) for Israel in ages 5–17 years (year 5). Small sample sizes (i.e., low case counts) in ages 5–-17 years also contribute to variable increases in each country population included. For example, in Israel, only one case of PCV20-13 serotype disease occurred in individuals ages 5–17 years in the year preceding PCV13.

DISCUSSION

We estimated the annual population-level impact of PCV13 NIPs on vaccine type and NVT IPD incidence across all ages using national surveillance data of countries that switched from PCV7 to PCV13 in their pediatric NIP. The percent reductions in IPD incidence of PCV13-7 serotypes and NVT serotypes for each year following PCV13 introduction were estimated for children and adults in five countries with established NIPs. PCV13-7 serotype IPD incidence decreased across all five countries and age groups, reaching a maximum reduction at about years 3–4 of the PCV13 program for ages < 5 years and years 4–5 post introduction for ages ≥ 5 years. For PCV13-7 serotypes, IPD incidence was reduced up to 93% among children targeted for vaccination and $\sim$ 60–80% among older age groups not targeted for vaccination, although with more variability across countries and among those ≥ 50 years of age.

The results suggest that pediatric PCV13 use provides rapid and substantial direct and indirect protection against IPD attributable to PCV13-7 serotypes compared to the year immediately before PCV13 introduction. We observed clear evidence of indirect protection among older age groups who are primarily unvaccinated. However, the impact of IPD incidence among unvaccinated age groups (ages ≥ 5 years) is smaller than the impact among age groups targeted for vaccination (< 5 years of age). Despite indirect effects from the pediatric PCV13 program, a substantial burden of PCV13-type pneumococcal disease persists. As such, direct vaccination of adults with higher valent PCVs may help further reduce the remaining burden.

PCV13-7 serotype IPD incidence reductions were greater when excluding serotype 3. Despite NIPs including PCV13, serotype 3 IPD may persist because of its unique immunologic characteristics compared to other PCV13 serotypes, persistent carriage in vaccinated children and therefore continued community-level transmission, and a shift in the predominant circulating clades [4, 9, 16, 18, 20, 35, 38]. PCV13 provides direct vaccine effectiveness against serotype 3 IPD in children, which has been estimated to be 50.5% (95% CI 8.2–73.3%) from a meta-analysis of PCV13 studies or 65.5% (95% CI 34.4–81.8%) from a recent pooled analysis of ten European sites (SpIDnet) [30, 32, 33]. PCV13 has also provided indirect population-level impact against serotype 3 in adults ≥ 65 years compared to impact in countries using PCV10 [34].

We speculate the rate of reduction and time to stabilization of IPD incidence across age groups and countries may be associated with multiple factors including vaccine schedule, implementation of a catch-up program, duration of PCV7 use, vaccine uptake, availability of an adult program, serotypes in circulation, and general epidemiologic variability. For example, Australia had a less substantial decrease in PCV13-7 incidence than other countries in the analysis, possibly related to the use of a PCV13 $3 + 0$ dosing schedule until year 7 (2018) when a $2 + 1$ dosing schedule was adopted. Among Australian children < 5 years, persistent vaccine-type IPD may be due to breakthrough cases, whereas older age groups not targeted for vaccination may have yet to receive full indirect protection through an infant vaccination program that includes a booster dose [2]. Additionally, IPD rates between Aboriginal and Torres Strait Islander compared with non-Indigenous Australians are disproportionately higher despite the recommendation of a $3 + 1$ dosing schedule. Household crowding and young age (< 1 year) remain increased risk factors for IPD, potentially contributing to

breakthrough cases. In Canada, we found that the indirect vaccine impact was also less pronounced than in some other countries. Although the reason cannot be determined, possible contributors include lower-than-average national vaccination uptake rate of routine PCV13 immunization, which was < 80% for 2 + 1 schedule completion in 2013 [14], and specifically in one large province, Ontario, which houses ~ 38% of the Canadian population, where rates ranged from 76%–79% between 2013–2016 [29]. Another potential contributing factor could be that PCV10 replaced PCV7 as the vaccine of choice in 2009 in four provinces briefly until 2011; therefore, incidence from serotypes 1, 5, and 7F may have been reduced slightly before the introduction of PCV13. The US had among the largest and most rapid reductions in IPD incidence, which was sustained across time in all age groups, which may be due to the 3 + 1 dosing schedule, duration of PCV7 use prior to PCV13 use, implementation of a PCV13 catch-up program in 2010, inclusion of an adult PCV13 NIP in 2014, or other programmatic differences compared with the other countries.

Increases in NVT IPD compared to the PCV7 period were observed in all age groups except in the US. Although the degree of increase varied by country and age group, results support use of higher valent PCVs to address emergence of NVT cases. As demonstrated in the England and Wales data, the overall decline in PCV13-type disease was offset by an increase in NVT IPD. Ladhani et al. reported that serotypes 8, 12F, and 9N were responsible for > 40% of IPD cases by 2016/17, which was consistently found across all age groups [21]. This is mirrored in other studies of serotype trends post-PCV13 introduction [17, 19, 22–24]. Similar findings are observed in Israel, where there is a growing problem of increasing IPD incidence due to NVT serotypes, but this did not offset the overall IPD reductions from PCV13 implementation [23]. Moreover, the five most common prevalent IPD serotypes found in Israel were 12F, 15B/C, 5, 19A, and 33F in 2011–2014 for children < 3 years of age [23]. The same NVT serotypes continued causing IPD more recently (during 2015–2016), such as 12F, 15B/C, and 33F as well as 27, 22F, 15A, 7B, 10A, and 10B [5], suggesting that PCV20 may help address some of the current unmet need. Based on change in incidence rates of PCV20-13, a higher-valent PCV will likely help reduce current pneumococcal disease burden across all ages for the countries included in this analysis. IPD isolate data in Israel have always been predominantly and consistently taken from medical health centers from admitted children, whereas this was not observed in the US. Changes in US blood culturing practice over the surveillance period have been hypothesized as an important contributor of the observed differences in NVT trends across countries. For example, Palmu et al. [25] proposed that incidence of NVT serotypes observed among admitted children in the US is similar to that observed for the other countries, suggesting that a differential bias (i.e., change in case ascertainment) may have occurred during surveillance over 2009–2017 (our analysis years). Data from US have not been stratified sufficiently to confirm this [25].

This study is subject to limitations. First, for the NVT serotypes, this serotype grouping includes over 80 different serotypes, and there may be heterogeneity across countries' respective NVT serotype distribution. There are serotypes that can be associated with more than one lineage which have an important role in serotype replacement in different countries. For example, serotype 12F is associated with GPSC55 in Israel and GPSC26 in South Africa and The Gambia, which can play important roles in anti-microbial resistance and invasiveness [23]. Second, we use a single year prior to the introduction of PCV13 to serve as the baseline for incidence changes following PCV13 introduction. As IPD incidence is rare and fluctuates from year to year, annual impact estimates can be unstable. Confidence intervals for IRRs could not be estimated because of lack of access to the appropriate data. Third, incidence for children < 5 years was used for children < 2 and 2–4 years, and data for adults ages 18–49 were used for ages 18–34 and 35–49 when these age-stratified data were unavailable, which may have misrepresented the age-specific changes in IPD over time. Finally, several country-specific variables were not considered in this analysis.

Duration of prior history of PCV7 use before PCV13 implementation, differing methods of IPD surveillance across countries (with incidence trend estimates potentially affected by the surveillance methodology), and variable regional and NIP characteristics may lead to differences in impact of the program. For example, vaccination uptake of the vaccine program, the vaccine dosing schedule, and the availability and uptake of an adult PCV program differ across countries.

CONCLUSION

Overall, our findings demonstrate PCV13-7 vaccine-type IPD incidence consistently decreased over time following introduction of PCV13 across countries and declines were more pronounced for the PCV13-7 grouping when excluding serotype 3. Non-PCV13 serotype incidence was variable by country and age group, which may be due to country-specific contextual variables. Countries with long-standing PCV13 infant NIPs have observed substantial direct and indirect benefits, which are demonstrated in this study by the reduction in PCV13-7 IPD incidence compared to the PCV7 period. Higher-valent PCVs are needed to address this emerging pneumococcal disease burden across all ages for the countries included in this analysis. Directly vaccinating both infant and adult populations may further reduce the overall population disease burden and prevent vaccine-type pneumococcal disease.

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