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The impact of the changing pneumococcal national immunisation program among older Australians

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ABSTRACT

Australia has a universal infant pneumococcal conjugate vaccination program and until recently a universal pneumococcal polysaccharide vaccine program for non-Indigenous adults aged ≥65 years and Indigenous adults aged ≥50 years. We documented the impacts of infant and adult vaccination programs on the epidemiology of invasive pneumococcal disease (IPD) in Indigenous and non-Indigenous adults.

IPD notifications from the National Notifiable Disease Surveillance System were analysed from 2002 to 2017, grouped by age, vaccine serotype group and Indigenous status. Since the universal funding of infant and elderly pneumococcal vaccination programs in January 2005, total IPD decreased by 19% in non-Indigenous adults aged ≥65 years but doubled in Indigenous adults aged ≥50 years. Vaccine uptake was suboptimal in both groups but lower in Indigenous adults. IPD due to the serotypes contained in the pneumococcal conjugate vaccines (PCV) except for serotype 3 declined markedly over the study period but were replaced by non-PCV serotypes. Serotype 3 is currently the most common in older adults. In the populations eligible for the adult 23-valent pneumococcal polysaccharide vaccine (23vPPV) program, IPD rates due to its exclusive serotypes increased to a lower extent than non-vaccine types. In 2017, non-vaccine serotypes accounted for most IPD in the older population eligible for the 23vPPV program, while it's eleven exclusive serotypes accounted for the majority of IPD in younger adults.

Infant and adult pneumococcal vaccination programs in Australia have shaped the serotype-specific epidemiology of IPD in older adults. IPD remains a significant health burden for the Indigenous population. Herd immunity impact is clear for PCV serotypes excluding serotype 3 and serotype replacement is evident for non-PCV serotypes. The adult 23vPPV immunisation program appears to have partially curbed replacement with IPD due to its eleven exclusive serotypes, highlighting a potential benefit of increasing adult 23vPPV coverage in Australia.

1. Introduction

Invasive pneumococcal disease (IPD) has a major impact on older adults. Two vaccines are widely licensed to protect this group – the 23-valent pneumococcal polysaccharide vaccine (23vPPV) and the 13-valent pneumococcal conjugate vaccine (13vPCV), and one or both of these are recommended or funded in most developed countries [1–3]. 23vPPV is effective in preventing IPD in older adults but evidence on its effectiveness against the more common non-invasive disease, primarily pneumonia, is mixed [4]. In contrast the 13vPCV has been shown to be moderately effective in preventing non-invasive pneumococcal pneumonia in adults [5]. Pneumococcal vaccine policy has changed markedly over time in Australia. 23vPPV was first recommended but not funded for high risk groups in 1986, then recommended for all adults 65 years and older and Indigenous adults 50 years and older in 1997. It was funded for Indigenous groups in 1999 and for all 65 years and over in 2005. In 2011 revaccination with 23vPPV was restricted to high risk individuals. 7vPCV was funded for high risk infants in 2001, was extended to all children in 2005, and then, replaced with 13vPCV in children in July 2011 [6] (Table 1). Although very high vaccination coverage has been attained in infants, with 95% reported for the 2016–17 birth cohort at 12 months [7], coverage in adults has been consistently subopti-

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Table 1
Significant events in pneumococcal vaccination practice in Australia [6]

Year	Intervention
1986	Unfunded vaccination recommended for individuals with specified underlying medical conditions that increase the risk of pneumococcal disease or complications, using either 23-valent pneumococcal polysaccharide vaccine (23vPPV) or 14-valent pneumococcal polysaccharide vaccine (14vPPV).
1997	Vaccination recommended for all adults aged >65 years and subsidised under the PBS. Vaccination recommended for all Aboriginal and Torres Strait Islander people aged 50 years. Revaccination with 23vPPV every 5 years recommended for Aboriginal and Torres Strait Islander people aged >50 years.
1999	23vPPV funded for all Aboriginal and Torres Strait Islander people aged >50 years and those aged 15–50 years with underlying medical conditions.
2003	7vPCV recommended for all infants at 2, 4 and 6 months of age. List of high-risk medical conditions for which a child became eligible for the nationally funded 7vPCV was expanded. 23vPPV revaccination/ booster dose recommendations changed to: • Non-Indigenous adults aged <65 years with underlying medical conditions or who were smokers should have a single booster at 65 years of age or 10 years after the 1st dose (whichever is later) • Non-Indigenous adults aged ≥65 years should have a single booster 5 years later • Aboriginal and Torres Strait Islander people aged 15–49 years with underlying medical conditions or who are smokers should have a booster dose 5 years after the 1st dose, with a subsequent booster dose at 50 years of age or 10 years after the first booster • Aboriginal and Torres Strait Islander people aged ≥50 years should have a single booster 5 years later
2005	Nationally funded 7vPCV program for all infants. 23vPPV funded for all adults aged ≥65 years.
2008	23vPPV revaccination/booster dose recommendations changed: • Non-Indigenous adults aged <65 years with underlying medical conditions or who are smokers should have a booster dose 5 years after the 1st dose, with a subsequent booster dose at 65 years of age or 5 years after the first booster • Aboriginal and Torres Strait Islander people aged 15–49 years with underlying medical conditions or who are smokers should have a booster dose 5 years after the 1st dose, with a subsequent booster dose at 50 years of age or 5 years after the first booster
2011	Revaccination with 23vPPV ceased temporarily, in response to increased number of reported injection site adverse events. 13vPCV replaced the 7vPCV at 2, 4 and 6 months of age. Revaccination with 23vPPV recommences but non-indigenous over 65 years with no medical conditions restricted to one booster.
2013	Multiple complex changes to booster doses of both 23vPPV and 13vPCV depending on age and indigenous status.
2018	Schedule for routine childhood vaccination with 13vPCV changed from 3+0 at 2, 4 and 6 months of age to 2+1 at 2, 4 and 12 months of age other than some groups of indigenous children who remained on 3+1 regime.
2020	A single dose of 13vPCV is recommended and funded for Indigenous adults at 50 years of age, followed by a dose of 23vPPV 12months later and a 2nd dose of 23vPPV 5–10 years after that. A single dose of 13vPCV is recommended and funded for non-Indigenous adults at 70 years of age, replacing the previously funded dose of 23vPPV at 65 years of age. A single dose of 13vPCV is recommended and funded for children and adults with specific conditions associated with very high risk of pneumococcal disease, followed by a dose of 23vPPV 12 months later and a 2nd dose of 23vPPV 5–10 years after that.

mal. In Australia there is no consolidiated national database for adult pneumoncoccal immunisation. Across the study period in New South Wales, Australia's most populous state, vaccination rates for non-Indigenous adults 65 years and older were between 45% – 63% and for Indigenous adults aged 65 years and older were between 26% – 45% [8,9]. Given that Australia has a national health system it can be reasonably assumed that these rates reported for New South Wales represent those nationally.

Understanding the impact of the changes to pneumococcal vaccination program over time is complicated. Use of conjugate vaccine in infants has been very effective in preventing vaccine-type IPD and non-invasive pneumococcal disease in vaccinated populations. Increases in non-vaccine type pneumococcal disease have been seen following widespread conjugate vaccine use, but overall rates of IPD due to any serotype have decreased in most settings [10,11]. There have been substantial herd immunity impacts in older age groups, but the overall decrease in IPD has been less marked than in children [10,12]. Previous analyses of IPD data up to 2011 have also shown a lower rate of increase in serotypes found only in the 23vPPV compared to non-vaccine types suggesting a direct impact from 23vPPV use but this was not statistically significant [12]. The direct impact of 23vPPV has not been examined in more recently published Australian studies. Australia has recently reviewed the adult pneumococcal program and a recommendation has been made to delay universal vaccination for non-Indigenous adults to age ≥ 70 years and to replace the currently recommended single dose of 23vPPV with a single dose of 13vPCV. An enhanced vaccination program, including one dose of 13vPCV followed by two doses of 23vPPV, has been recommended for Indigenous adults aged ≥ 50 years and other adults newly diagnosed with a condition that places them at very high risk of pneumococcal disease [13]. Table 1 describes the significant events in pneumococcal vaccination practice in Australia since 1986.

In this context, the aim of this study is to examine the epidemiology of IPD in Indigenous and non-Indigenous Australians, with a particular focus on adults, up to 6.5 years after the introduction of the 13vPCV for infants. Using serotype groups related to the different vaccines we aim to describe the impacts of vaccine policy over time and highlight the serotype specific epidemiology of current pneumococcal disease.

2. Methods

IPD notifications for 2002 to 2017 were obtained from the National Notificable Disease Surveillance System (NNDSS). NNDSS IPD data, current as at 16/08/2018, were provided by the Office of Health Protection, Department of Health, on behalf of the Communicable Diseases Network Australia. Only laboratory confirmed IPD cases are notifiable, that is *Streptococcus. pneumoniae* in a normally sterile site, such as blood or cerebrospinal fluid either by culture or by nucleic acid amplification testing.

The main focus of the analysis was on cases within four adult groups which allowed comparison of IPD trends in non-Indigenous and Indigenous populations eligible (groups 1 and 3) or not eligible (groups 2 and 4) for the adult pneumococcal vaccination program:

(1) cases aged ≥ 65 years recorded as non-Indigenous or with unknown Indigenous status (23vPPV funded).
(2) cases aged 50 to 64 years recorded as non-Indigenous or with unknown Indigenous status (23vPPV not funded).
(3) cases recorded as Indigenous and aged ≥ 50 years (23vPPV funded), and
(4) cases recorded as Indigenous and aged 25 to 49 years (23vPPV funded only for the medically at risk).

For the purpose of these analyses, IPD cases with unknown Indigenous status were assumed to be non-Indigenous. This assumption was consistent with the vast majority (88%) of IPD cases with known indigenous status occurring in the non-Indigenous population.

Serotypes were grouped as follows for analysis of the non-Indigenous sample:

(1) 7vPCV only serotypes (4, 6B, 9V, 14, 18C, 19F, 23F);
(2) 13vPCV not 7vPCV not 3 serotypes (1, 5, 6A, 19A, 7F);
(3) serotype 3;

(4) 23vPPV only serotypes (2, 8, 9 N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F); and
(5) non-vaccine covered serotypes (NVT).

Serotype 3 was isolated because of evidence of lower effectiveness of both vaccines against this serotype compared to others [14]. In the Indigenous sample serotype 1 was also separated out from the 13vPCV-not7v not 3 types due to an outbreak of serotype disease which occurred in 2010–11 [15]. IPD cases where serotype data was not available were included in the analyses of total IPD only but were excluded from the analyses of the distribution of IPD serotypes.

Annual IPD rates were calculated using the estimated resident populations from the Australian Bureau of Statistics [16]. Data for the Indigenous population were grouped into two-year periods to increase analytical power.

Incident rate ratios (IRR) post– versus pre–vaccine introduction were the metric used to compare the different vaccine policy periods (pre-7vPCV, post 7vPCV and pre-13vPCV and post-13vPCV), with 95% confidence intervals. Average IPD incidence in the 3 years preceding 7vPCV vaccine introduction represented the baseline pre-7vPCV data for the non-Indigenous population. Data were not available for the period before the introduction of the 7vPCV for Indigenous infants in 2001, so the earliest available datapoint, corresponding to 2002–03 period was used instead, during which time PCV coverage in Indigenous infants was low (33%) and minimal herd protection was expected. As the 13vPCV program was initiated in July 2011, IPD incidence in 2011 was assumed to represent both the latest available post-7vPCV datapoint and the baseline pre-13vPCV data point for IRR calculations, noting November 2011 would be the earliest possible date by which the full 2, 4 and 6 month 13vPCV infant schedule could be completed. IPD incidence in 2017 represented the last available post-13vPCV data point for IRR calculation. All analyses were performed using Stata 14.2 (StataCorpLLC, College Station, TX, USA).

No ethical clearance was requested since the study only involved anonymised data from the Communicable Disease Network Australia, of which the majority are publicly available from 2009 and are otherwise available on request.

3. Results

3.1. Study sample

Between 2002 and 2017 there were 28,434 IPD notifications, of which 3,094 (11%) were reported as Indigenous, 21,953 (77%) were reported as non-Indigenous, and 3,390 (12%) were reported as unknown Indigenous status. As noted above, for the purpose of these analyses, IPD cases with unknown Indigenous status are assumed to be non-Indigenous and will be referred as such hereafter. Of the non-Indigenous notifications, 8876 (35%) were in the population aged ≥65 years, and 4953 (20%) were in the population aged 50 to 64 years. Of the Indigenous notifications, 727 (23%) were in the population aged ≥ 50 years and 1,273 (41%) were in the population aged 25 to 49 years. Overall, serotype data were available for 92% of notifications.

3.2. Age distribution

Rates of IPD in 2017 (non-Indigenous) or 2016–17 (Indigenous) were highest in young children and older adults, and substantially higher in Indigenous compared to non-Indigenous people in every age group. The disparity in IPD rates between non-Indigenous and Indigenous populations was most marked in adults from the age of 25 years onwards (Fig. 1).

3.3. Trends of serotype-specific IPD incidence in non-Indigenous adults

Fig. 2 shows the trends in serotype specific IPD incidence rates in non-Indigenous adults aged 50–64 or ≥65 years, grouped by vaccine type, with the exception of serotype 3, from 2002 until 2017. The figure demonstrates the herd immunity and replacement impact of the infant PCV program in both age groups. IPD due to 7vPCV serotypes declined markedly between the 2002–04 baseline and 2011 in both age groups with corresponding IRRs (2011:2002–04) of 0.15 (95% CI: 0.10–0.21) and 0.10 (0.07–0.14) in adults aged 50–64 and ≥65 years respectively, remaining stable thereafter (Table 1). IPD due to the additional serotypes in 13vPCV excluding serotype 3 increased between 2002 and 04 and 2011 [$IRR_{2011:2002-04}$ = 4.0 (2.9–5.5) in adults aged 50–64 and $IRR_{2011:2002-04}$ = 2.7 (2.1–4.4) in adults ≥ 65 years] and declined after implementation of the 13vPCV infant program [$IRR_{2017:2011}$ = 0.35 (0.24–0.51) in adults aged 50–64 and $IRR_{2017:2011}$ = 0.25 (0.18–0.35) in adults ≥ 65 years]. In contrast, IPD due to serotype 3, which was the most common serotype in 2017, increased throughout the study period, [$IRR_{2017:2002-04}$ = 2.75 (1.80–4.23) in adults aged 50–64, $IRR_{2017:2002-04}$ = 2.20 (1.67–2.90) in adults ≥ 65 years] (Table 1). IPD due to non-PCV serotypes increased from the 2002–04 baseline in both age groups. However, in the group aged ≥65 years, eligible for 23vPPV, the $IRR_{2017:2002-04}$ for IPD attributable to its 11 exclusive serotypes [$IRR_{2017:2002-04}$ = 2.2 (1.8–2.7)] was significantly lower than the $IRR_{2017:2002-04}$ for IPD attributable to non-vaccine serotypes [IRR = 6.3 (5.0–8.1)], resulting in higher incidence of the latter from 2009. A similar crossover was not observed in the population aged 50–64, in which the observed increases in IPD rates were similar for both non-PCV groups, and the incidence of IPD attributable to the exclusive serotypes in 23vPPV remained above that of non-vaccine serotypes throughout the study period (Fig. 2 and Table 2).

Overall, there was no change in the incidence of total IPD in non-Indigenous adults aged 50–64 years over the study period. In the older population aged ≥65 years total IPD decreased significantly from 2002 to 04 to 2011 and, although it again increased significantly by 2017, it remained 19% below the 2002–04 estimate [$IRR_{2017:2002-04}$ = 0.81 (0.74–0.88)] (Table 1).

IPD incidence rates and post: pre-immunisation IRRs by vaccine-type serotype groups for non-Indigenous children and younger adults aged < 50 years are presented in Supplementary Table 1.

3.4. Trends of serotype-specific IPD incidence in Indigenous adults

Fig. 3 shows the trends in serotype specific IPD incidence rates in Indigenous adults aged 25–49 years and greater than 50 years grouped by vaccine type, with the exception of serotypes 3 and 1 from 2002–03 until 2016–17. In Indigenous adults yearly rates were more variable, reflecting lower population numbers, but the overall trends were similar to the non-Indigenous population. The reduction in IPD due to 7vPCV serotypes between 2002–03 and 2010–11 was less evident than in the non-Indigenous population, and from a lower base, but was statistically significant in the population aged ≥ 50 years [$IRR_{2010-11:2002-03}$ = 0.22 (0.05–0.73)] (Table 1). IPD due to the additional serotypes in 13vPCV excluding serotype 3 and serotype 1 increased from 2002–03 to 2010–11 in the population aged ≥ 50 years [$IRR_{2010-11:2002-03}$ = 4.5 (1.3–23.8), and declined in both populations after implementation of the 13vPCV infant program [$IRR_{2016-17:2010-11}$ = 0.28 (0.13–0.57) in adults aged 25–49 and $IRR_{2016-17:2010-11}$ = 0.49 (0.22–1.03) in adults ≥ 50 years] (Table 1). The serotype 1 epidemic in remote Australia is evident from 2010 to 2013 in both age-groups. Statistically significant increases were seen in the 23vPPV-only and non-vaccine serotypes over time in the population aged ≥ 50 years

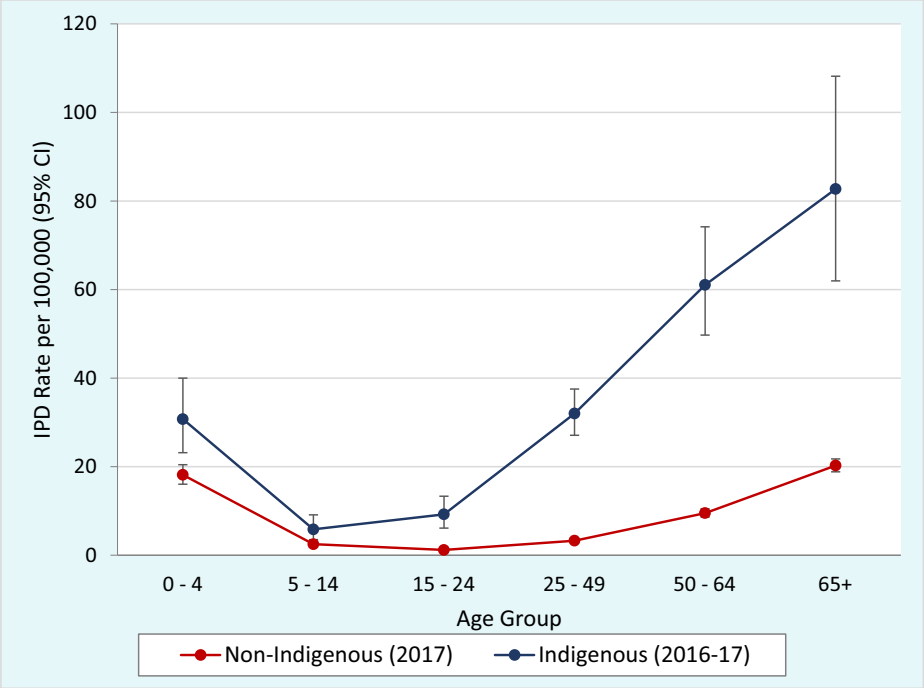

Fig. 1. IPD notification rate by age group and Indigenous status.

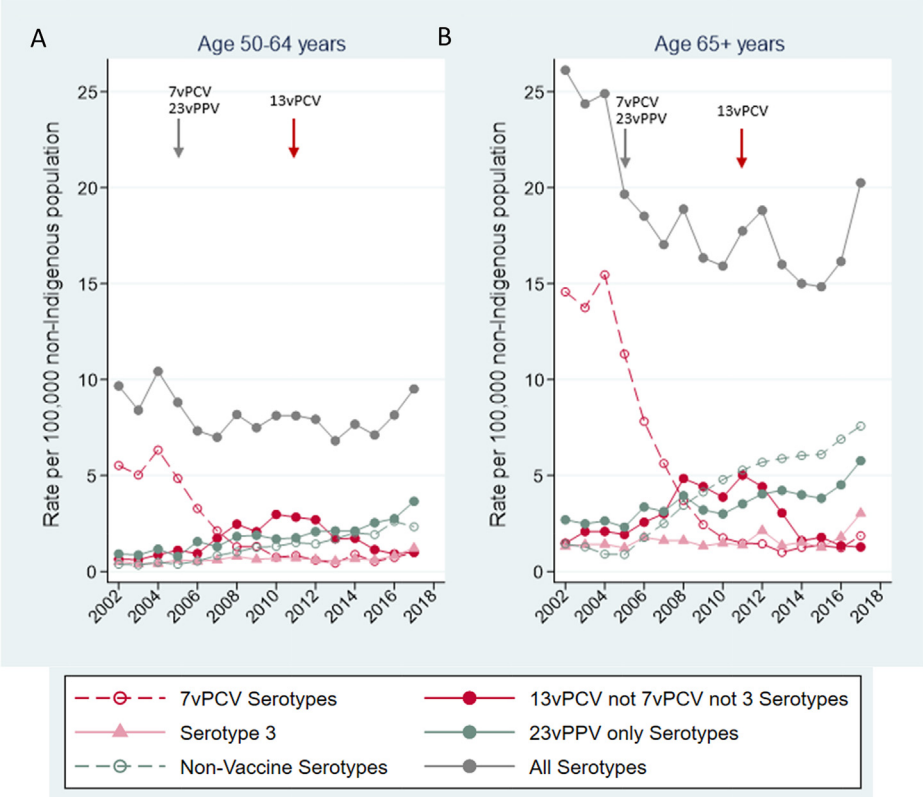

Fig. 2. IPD rates among non-Indigenous adult Australians aged 50–64 years (Panel A) or aged ≥65 years (Panel B) by serotype grouping, 2002–2017.

[$IRR_{2016\text{-}17:\ 2002\text{-}03}$ = 3.3 (1.4–9.6) for IPD due to 23vPPV-only and $IRR_{2016\text{-}17:\ 2002\text{-}03}$ = 7.9 (2.9–29.8) for IPD due to non-vaccine serotypes], but not in the younger age group.

Overall, in Indigenous adults aged 25–49 years total IPD increased significantly from 2002–03 to 2010–11 and decreased by 2016–2017 so that there was no significant difference in rates from 2002 to 03 to 2016–17. In contrast, in the older population, total IPD rates approximately doubled over the study perid, with most of the increase observed betweeen 2002–03 and 2010–11, prior to the introduction of the infant 13vPCV program (Table 1).

Table 2
IPD incidence rates and Post: Pre-immunisation rate ratios by Indigenous status in Australian adults.

Age	Serotype group	Incidence /10^5			IRR (95% CI)	p value	IRR (95% CI)	p value	IRR (95% CI)	p value
Non-Indigenous										
		2002–04	**2011**	**2017**	**2011:2002–04**		**2017:2011**		**2017: 2002–04**	
50–64	All IPD	9.51	8.12	9.51	0.85 (0.75–0.97)	0.0136	1.17 (1.01–1.36)	0.0335	1.00 (0.89–1.12)	0.9931
	7vPCV	5.64	0.83	0.97	0.15 (0.10–0.21)	<0.0001	1.18 (0.73–1.93)	0.4717	0.17 (0.12–0.24)	<0.0001
	13vPCV not 7vPCV not 3	0.71	2.83	1.00	4.01 (2.94–5.49)	<0.0001	0.35 (0.24–0.51)	<0.0001	1.42 (0.95–2.11)	0.0755
	Serotype 3	0.44	0.70	1.21	1.59 (0.95–2.63)	0.0595	1.73 (1.07–2.84)	0.0181	2.75 (1.80–4.23)	<0.0001
	23vPPV only	0.98	1.75	3.66	1.79 (1.29–2.46)	0.0003	2.08 (1.56–2.80)	<0.0001	3.72 (2.87–4.85)	<0.0001
	Non-Vaccine	0.40	1.50	2.33	3.77 (2.48–5.79)	<0.0001	1.55 (1.11–2.17)	0.0067	5.84 (3.99–8.69)	<0.0001
65+	All IPD	25.13	17.75	20.25	0.71 (0.64–0.78)	<0.0001	1.14 (1.02–1.28)	0.0185	0.81 (0.74–0.88)	<0.0001
	7vPCV	14.6	1.46	1.86	0.10 (0.07–0.14)	<0.0001	1.27 (0.86–1.89)	0.2128	0.13 (0.10–0.16)	<0.0001
	13vPCV not 7vPCV not 3	1.88	5.02	1.28	2.67 (2.11–3.38)	<0.0001	0.25 (0.18–0.35)	<0.0001	0.68 (0.48–0.95)	0.0175
	Serotype 3	1.38	1.37	3.03	1.00 (0.68–1.44)	0.9926	2.21 (1.54–3.24)	<0.0001	2.20 (1.67–2.90)	<0.0001
	23vPPV only	2.60	3.52	5.78	1.35 (1.06–1.72)	0.0130	1.63 (1.30–2.08)	<0.0001	2.22 (1.8–2.70)	<0.0001
	Non-Vaccine	1.20	5.29	6.90	4.39 (3.38–5.75)	<0.0001	1.43 (1.18–1.75)	<0.0001	6.30 (4.96–8.09)	<0.0001
Indigenous										
		2002–03	**2010–11**	**2016–17**	**2010–11:2002–03**		**2016–17:2010–11**		**2016–17: 2002–03**	
25–49	All IPD	36.66	45.79	31.99	1.25 (0.99–1.57)	0.0495	0.70 (0.56–0.87)	0.0010	0.87 (0.69–1.11)	0.2542
	7vPCV	6.11	4.38	4.27	0.72 (0.36–1.40)	0.3001	0.97 (0.49–1.95)	0.9309	0.70 (0.36–1.34)	0.2484
	13vPCV not 7vPCV not 3 not 1	6.94	8.28	2.35	1.19 (0.69–2.09)	0.5081	0.28 (0.13–0.57)	0.0001	0.34 (0.15–0.71)	0.0019
	Serotype 1	1.94	6.82	0	3.51 (1.50–9.51)	0.0012	0.00 (0.00–0.12)	<0.0001	0.00 (0.00–0.53)	0.0029
	Serotype 3	1.67	0.73	1.07	0.44 (0.07–2.05)	0.2554	1.46 (0.28–9.40)	0.6303	0.64 (0.15–2.52)	0.4749
	23vPPV only	9.72	12.18	13.86	1.25 (0.80–1.99)	0.3082	1.14 (0.77–1.68)	0.4935	1.43 (0.93–2.21)	0.0883
	Non-Vaccine	8.33	11.94	7.89	1.43 (0.89–2.34)	0.1201	0.66 (0.42–1.03)	0.0573	0.95 (0.57–1.59)	0.8223
50+	All IPD	33.08	62.74	67.10	1.89 (1.29–2.82)	0.0004	1.07 (0.83–1.38)	0.5949	2.03 (1.41–2.97)	<0.0001
	7vPCV	10.45	2.32	4.79	0.22 (0.05–0.73)	0.0059	2.06 (0.61–8.88)	0.2168	0.46 (0.18–1.14)	0.0670
	13vPCV not 7vPCV not 3 not 1	2.61	11.62	5.66	4.45 (1.32–23.38)	0.0061	0.49 (0.22–1.03)	0.0434	2.16 (0.59–11.86)	0.2247
	Serotype 1	0.87	6.97	0	8.01 (1.18–342.32)	0.0139	0.00 (0.00–0.27)	<0.0001	0.00 (0.00–19.52)	0.3336
	Serotype 3	1.74	4.65	7.84	2.67 (0.53–25.80)	0.2131	1.69 (0.70–4.49)	0.2194	4.50 (1.08–40.03)	0.0208
	23vPPV only	5.22	13.36	17.42	2.56 (1.01–7.68)	0.0311	1.30 (0.76–2.28)	0.3123	3.34 (1.41–9.63)	0.0020
	Non-Vaccine	3.48	20.91	27.45	6.01 (2.15–23.22)	<0.0001	1.31 (0.86–2.04)	0.1926	7.88 (2.93–29.82)	<0.0001

IPD incidence rates and post: pre-immunisation IRRs by vaccine-type serotype groups for Indigenous children and younger adults aged < 2 years are presented in Supplementary Table 2.

3.5. Vaccine-preventable IPD

Fig. 4 and Fig. 5 illustrate the distribution of IPD serotypes at the start of the study period, at the time of implementation of the 13vPCV infant program and at the end of the study period in the adult non-Indigenous and Indigenous populations, respectively. The proportion of IPD attributable to serotypes included in the 13vPCV (excluding serotype 3) has decreased over time in all populations examined while those preventable only by the 23vPPV and non-vaccine serotypes have increased markedly. By the final period examined 13vPCV-non-3 serotypes account for 23% and 17% of IPD in non-Indigenous populations aged 50–64 and ≥ 65 years, and for 22% and 17% in the Indigenous population aged 25–49 years ≥ 50 years, respectively. Serotype 3 is currently the most common serotype in non-Indigenous adults and Indigenous adults aged ≥ 50 years, while serotype 8 (in 23vPPV but not 13vPCV) is the most common in the Indigenous population aged 25–49. The eleven serotypes included only in the 23vPPV currently account for the majority of IPD in the adult populations that are not eligible for the 23vPPV program, representing 40% in non-

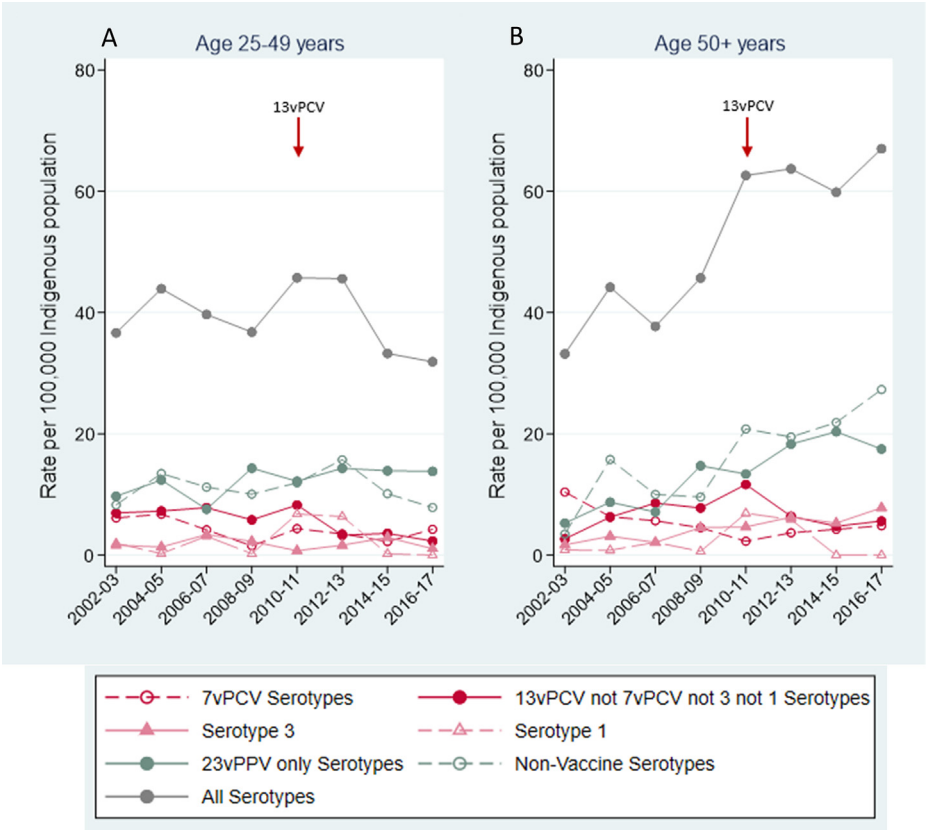

Fig. 3. IPD rates among Indigenous adult Australians aged 25–49 years (Panel A) or aged ≥50 years (Panel B) by serotype grouping, 2002–2017.

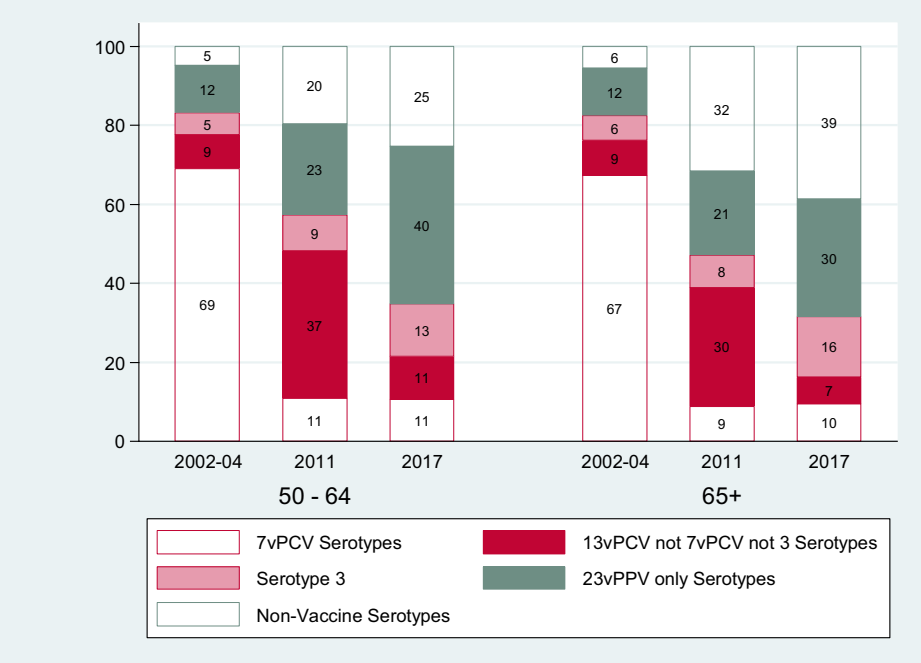

Fig. 4. Change in distribution of IPD notification rates by serotype subgroup and age group in non-Indigenous adults. The percentage of IPD notifications are expressed as a proportion of cases with known serotype.

Indigenous adults aged 50–64 and 47% in Indigenous adults aged 25 to 49 years. In contrast, the non-vaccine serotypes account for the majority of current IPD in the older populations eligible for the 23vPPV program, representing 39% of IPD in the non-Indigenous population aged ≥ 65 years and 43% of IPD in the Indigenous population aged ≥ 50 years.

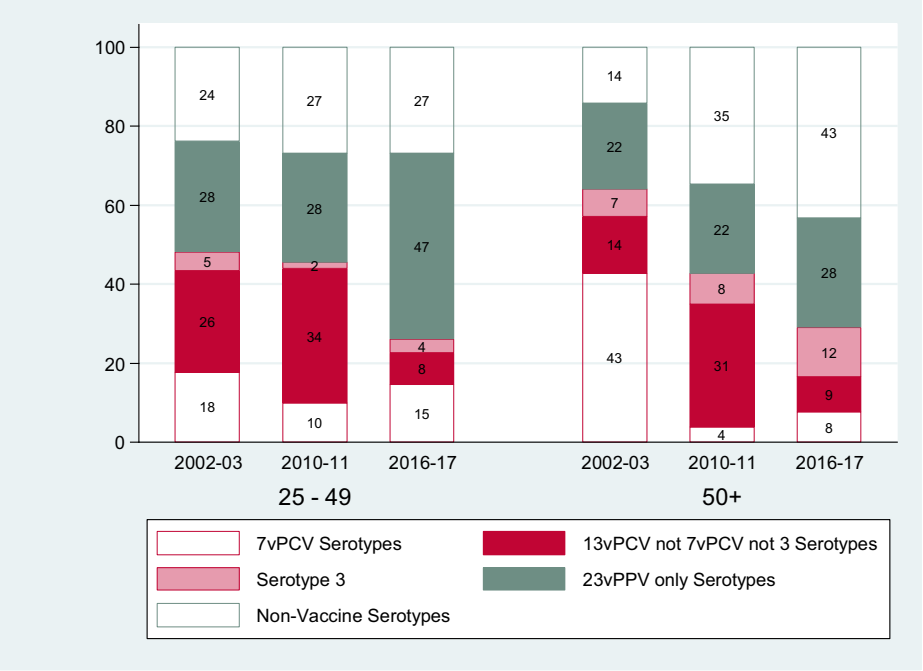

Fig. 5. Change in distribution of IPD notification rates by serotype subgroup and age group in Indigenous adults. The percentage of IPD notifications are expressed as a proportion of cases with known serotype.

4. Discussion

Since the funding of infant and elderly pneumococcal vaccination programs in Australia in January 2005, total IPD rates in the non-Indigenous elderly have decreased by 19%. This study has shown that the switch to higher valency conjugate vaccine in infants in 2011 was followed by a decrease in IPD due to the additional serotypes in 13vPCV other than serotype 3 in non-Indigenous Australians aged $\geq$ 65 years. However increases in non-PCV serotypes have continued, blunting the impact on overall IPD rates. IPD rates due to 23vPPV-only serotypes increased progressively over the study period but to a significantly lower extent than non-vaccine types, suggesting a direct impact from 23vPPV use in this age group. In the 50–64 year age group, where 23vPPV is not funded, there was no change in the incidence of total IPD over the study period, with a significantly greater increase in 23vPPV-only IPD compared to the older age group.

In Indigenous adults aged 25–49 years the rate of total IPD did not significantly change over the study period, while in Indigenous adults aged $\geq$ 50 years, total IPD rates have doubled. Herd immunity impacts from conjugate vaccine use in infants are evident, and there is a suggestion of an impact from 23vPPV use in Indigenous adults aged $\geq$ 50 years but this is not statistically significant. Likely explanations for the different impact on total IPD include that 7vPCV-type IPD include a smaller proportion of total IPD in Indigenous compared to non-Indigenous older adults at the start of the study (43% vs 67% of IPD cases with known serotype), the decrease in 7vPCV serotypes was less (7vPCV $IRR_{2016\text{-}17:2002\text{-}03}$ = 0.46 vs $IRR_{2017:2002\text{-}04}$ = 0.13), and the increase in non-vaccine types was greater ($IRR_{2016\text{-}17:2002\text{-}03}$ = 7.88 vs $IRR_{2017:2002\text{-}04}$ = 6.30), although these differences are not statistically significant.

Decreases in vaccine-type IPD in the elderly following high coverage infant conjugate pneumococcal vaccination have been observed in almost every setting that has been studied.[17] However non-conjugate-vaccine type IPD has continued to increase after initial introduction and also after their replacement by higher valency conjugate vaccines. Decreases in total IPD in the elderly have been seen in most but not all settings. Factors affecting these differing overall outcomes include the serotype distribution prior to infant vaccination, the time since the introduction of infant vaccination as the full impacts take around nine years,[18] the patterns of serotype replacement and the extent of 23vPPV use in the elderly.

Both a conjugate (13vPCV) and a polysaccaharide (23vPPV) vaccine are licensed for use in adults in most developed countries, and different choices have been made about which vaccine(s) to fund in different settings. Recently the continued use of 23vPPV in adults has been reviewed by the Pharmaceutical Benefit Advisory Committee (PBAC) in Australia and the Advisory Committee on Immunization Practices (ACIP) in the Unites States. Starkly different recommendations have been made by these committees. In Australia the PBAC have recommended that 23vPPV immunisation be limited to cohorts that have very high risk of pneumococcal infection, including Indigenous populations, and that healthy non-Indigenous adults $\geq$ 70 years be immunized with 13vPCV instead [13], thus removing universal 23vPPV from the schedule.

In contrast, in the United States, which implemented sequential immunisation with 13vPCV followed by 23vPPV for all adults aged $\geq$ 65 years in 2014, the ACIP has recently changed their guidance from a recommendation to use 13vPCV in older persons to making it a shared clinical decision-making, while maintaining the universal recommendation for 23vPPV in adults aged $\geq$ 65 years [19]. The major reason for this change was that non-13vPCV serotypes make up most of the pneumococcal disease burden [20] as they do in Australia, and that the majority of residual 13vPCV disease in this age group was due to serotype 3 against which the vaccine is relatively ineffective. The introduction of 13vPCV to the older persons schedule had little impact and was deemed not cost effective [21]. The ACIP also noted that adult coverage rates of 23vPPV were relatively low and that benefit might be obtained if adult immunization rates were improved. Other developed countries such as Germany, the United Kingdom and Canada

have also published detailed reviews of the cost effectiveness of adult pneumococcal vaccine programs, and continue to support adult 23vPPV immunisation. [22–24]

The recent PBAC recommendation differs from the approach of other developed countries. It also appears at odds with the results of our study, which demonstrates most remaining IPD in both Indigenous and non-Indigenous Australian adults is attributable to non-13vPCV serotypes and shows a moderating impact of the current 23vPPV program on serotype replacement. It will therefore be important to closely monitor the incidence of pneumococcal disease to determine the impact of this proposed change.

Most worryingly, the list of high risk conditions for whom PBAC has said 23vPPV should be recommended and funded [25], is missing most of the significant and most populous risk groups. Diabetics are known to be at risk of pneumococcal disease and data from England showed that the excess all-aged rate ratio decreased from 1.92 to 1.68 in the years after the commencement of a 23vPPV program. Diabetics are not covered for vaccine under the recent PBAC recommendations [26]. In a retrospective cohort study of over 56,000 people the excess hazard ratio for pneumonia in persons living with cardiovascular disease varied from 2.03 for persons living with coronary artery disease to 4.11 for those living with heart failure, with an overall hazard ratio for those living with cardiovascular disease of 2.27. The risk was even higher for those living with hypertension. These groups will not be covered for funded 23vPPV [27]. Other groups at higher risk of pneumococcal disease such as asthmatics and those with non-suppurative chronic obstructive airwarys disease are also outside the recommended “high risk” groups outlined by the PBAC [28]. All of these groups will only receive a dose of 13vPCV at 70 years, a policy seen over a 4 year trial in the United States to not impact on disease rates.

Furthermore, the complexity of the recommended protocol is likely to reduce pneumococcal vaccination coverage.[8] In Australia the 23vPPV coverage in those aged ≥65 years has decreased in the most populous state of New South Wales from 63% to 47% since the removal of the recommendation for a second dose in 2011 [9]. National coverage in Indigenous adults has always been poor, and in 2012–13 was estimated at 13% in the at-risk population aged 18 to 49 years, 23% in the population aged 50–64 years and 44% in those aged ≥65 years.[29] Therefore in Australia, given the small remaining numbers of IPD due to 13vPCV serotypes, rather than reducing access to 23vPPV, it is the opinion of the authors an alternative option for preventing IPD would be to increase coverage of 23vPPV. Additional protection would also be possible with a program of booster dosing with 23vPPV. Disease rates increase with increasing age and revaccination is likely to produce long term antibody levels consistent with primary vaccination [30]. Boosting at an interval of 5 years minimises the increase in self-limiting adverse events seen with re-vaccination [31].

At this time the development of both 15- and 20-valent conjugate vaccine candidates is well advanced [32–34]. From the data presented in this study no currently licensed vaccine is effective against serotype 3. This is a significant challenge in the development of the new conjugate vaccines. In this context, a study comparing the immungenity of prototype 15vPCV vaccines (Merck & Co., Inc., USA) against 13vPCV demonstrated greater opsonophagocytic activity geometric mean titers and IgG geometric mean concentrations [32]. Efficacy studies are needed to determine if this improved immunogenicity against serotype 3 observed in the 15vPCV formulations translates into protection against serotype 3 disease in immunised subjects. Furthermore, the results of the current study would suggest that despite increased serotype valency in new conjugate vaccines subsequent serotype replacement with nonconjugate vaccine serotypes can be expected.

This study has several potential limitations. Firstly it relies on laboratory diagnosis and notification of invasive disease, which may result in under-estimation of the true disease burden. Improvements in laboratory testing methods over time may result in increased sensitivity in detecting cases. Secondly, the lack of a national database of adult pneumococccal immunisation coverage introduces a complexity in interpreting the IPD incidence data; but drawing on what coverage data is available, the rates were consistently low for both non-Indigenous and Indigenous people over the study period with coverage being poorer in Indigenous people. However, it is possible that had 23vPPV coverage been higher in both groups, greater vaccine effectiveness against IPD due to its exclusive serotypes might have been observed.

In conclusion, substantial herd protection is evident as a result of the introduction of PCVs in infants but this is restricted to 12 of the 13 serotypes in 13vPCV - there is no vaccine effect for serotype 3. There is increasing IPD disease in adults due to non-PCV serotypes, which have been moderated to some extent as a result of 23vPPV. However coverage is suboptimal and hence greater benefits may be possible if greater coverage of 23vPPV was encouraged. Non-vaccine type IPD continues to increase, hence the need for investment in new vaccines with greater valencies. However, it is predicted that serotype replacement with nonconjugate vaccine serotypes will contine to occur.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

R Menzies: RM has no conflict of interests to declare.

A Stein: AS is an employee of Seqirus (Australia) Pty Ltd and owns shares in CSL Pty Ltd.

R Booy: RB receives funding from Baxter, CSL/Seqirus, GSK, Merck, Novartis, Pfizer, Roche, Romark, and Sanofi Pasteur for the conduct of sponsored research, travel to present at conferences, or consultancy work. All funding received is directed to research accounts at The Children’s Hospital at Westmead.

P Van Buynder: PVB is a member of the Seqirus Australia Pneumococcal Advisory Board and has received support for research and education from both Seqirus and Pfizer.

J Litt: JL is a member of the Seqirus Australia Pneumococcal Advisory Board. He has received financial support to run seminars on adult immunisation, including pneumococcal immunisation.

A W Cripps: AWC is a member of the Seqirus Australia Pneumococcal Advisory Board and the Merck & Co Global Pneumococcal Advisory Board. Seqirus Australia provided financial support for AWC to attend the Communicable Diseases Control 2019 Conference in Canberra, Australia.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.12.025.

References

[1] Bonnave C, Mertens D, Peetermans W, Cobbaert K, Ghesquiere B, Deschodt M, et al. Adult vaccination for pneumococcal disease: a comparison of the national guidelines in Europe. Eur J Clin Microbiol Infect Dis 2019;38:785–91.

[2] Huijts S. Vaccines to prevent pneumococcal community-acquired pneumonia. Clin Chest Med 2018;39:733–52.

[3] Control ECfDPa. Vaccine scheduler: Vaccine schedules in all countries of the European Union 2019. 2019.
[4] Van Buynder PG, Booy R. Pneumococcal vaccination in older persons: where are we today?. Pneumonia 2018;10:1.
[5] Bonten M, Huijts SM, Bolkenbaas M, Bolkenbaas M, Webber C, Grobbee DE. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med 2015;372:1114–25.
[6] National Centre for Immunisation Research and Surveillance. Significant events in pneumococcal vaccination practice in Australia; 2018.
[7] National Centre for Immunisation Research and Surveillance. Coverage data and Reports; vaccine coverage estimates – all children. 2019.
[8] Australian Institute of Health and Welfare. 2009 Adult Vaccination Survey. Canberra; 2011.
[9] HealthStats NSW. Influenza and pneumococcal disease immunisation; 2019.
[10] Meder KN, Jayasinghe S, Beard F, Dey A, Kirk M, Cook H, et al. Long-term impact of pneumococcal conjugate vaccines on invasive disease and pneumonia hospitalisations in Indigenous and non-Indigenous Australians. Clin Infect Dis 2019:ciz731.
[11] Corvisy R, Enhanced Invasive Pneumococcal Disease Surveillance Working Group. Invasive Pneumococcal Disease Surveillance, 1 January to 31 March 2019. In: Australian Department of Health, editor.
[12] Menzies R, Jayasinghe S, Krause V, Chiu C, McIntyre P. Impact of pneumococcal polysaccharide vaccine in people aged 65 years or older. Med J Aust 2014;200:112–5.
[13] Pharmaceutical Benefits Advisory Committee. July 2019 PBAC meeting - Other matters - Pneumococcal vaccines in adults. In: Australian Government Department of Health, editor; 2019.
[14] Jayasinghe S, Menzies R, Chiu C, Toms C, Blyth CC, Krause V, et al. Long-term Impact of a "3 + 0" Schedule for 7- and 13-Valent Pneumococcal Conjugate Vaccines on Invasive Pneumococcal Disease in Australia, 2002-2014. Clinical Infectious Diseases.64:175-83.
[15] Lai JYR, Cook H, Yip T-W, Berthelsen J, Gourley S, Krause V, et al. Surveillance of pneumococcal serotype 1 carriage during an outbreak of serotype 1 invasive pneumococcal disease in central Australia 2010–2012. BMC Infect Dis 2013;13:409.
[16] Australian Bureau of Statistics. Australian Demographic Statistics, Dec 2018. 2018.
[17] Feikin DR, Kagucia EW, Loo JD, Link-Gelles R, Puhan MA, Cherian T, et al. Serotype-specific changes in invasive pneumococcal disease after pneumococcal conjugate vaccine introduction: a pooled analysis of multiple surveillance sites. PLoS Med. 2013;10:e1001517.
[18] Shiri T, Datta S, Madan J, Tsertsvadze A, Royle P, Keeling MJ, et al. Indirect effects of childhood pneumococcal conjugate vaccination on invasive pneumococcal disease: a systematic review and meta-analysis. The Lancet Global Health.5:e51-e9.
[19] Advisory Committee on Immunization Practices. June 2019 meeting recommendations. Centres for Disease Control and Prevention; 2019.
[20] Advisory Committee on Immunization Practices. ACIP Presentation Slides: June 2019 Meeting. Centres for Disease Control and Prevention; 2019.
[21] Matanock A, Lee G, Gierke R, Kobayashi M, Leidner A, Pilishvili T. Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine Among Adults Aged ≥65 Years: Updated Recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep November 22.
[22] Falkenhorst G, Remschmidt C, Harder T, Wichmann O, Glodny S, Hummers-Pradier E, et al. Background paper to the updated pneumococcal vaccination recommendation for older adults in Germany. Bundesgesundheitsbl. 2016;59:1623–57.
[23] Joint Committee on Vaccines and Immunisation. Interim JCVI statement on adult pneumococcal vaccination in the UK. In: Department of Health and Social Care, editor.2015.
[24] National Advisory Committee on Immunization. Update on the use of pneumococcal vaccines in adults 65 years of age and older – A Public Health Perspective. Government of Canada; 2018.
[25] Pharmaceutical Benefits Scheme. Cost-effectiveness review of pneumococcal vaccines for the National Immunisation Program (NIP) – July 2019 PBAC Meeting; 2019.
[26] Seminog O, Goldacre M. Risk of pneumonia and pneumococcal disease in people hospitalized with diabetes mellitus: English record-linkage studies. Diabet Med 2013;30:1412–9.
[27] Yeh J-J, Lin C-L, Kao C-H. Relationship between pneumonia and cardiovascular diseases: a retrospective cohort study of the general population. Eur J Int Med 2019;59:39–45.
[28] Torres A, Blasi F, Dartois N, Akova M. 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.
[29] Webster F, Gidding H, Matthews V, Taylor R, Menzies R. What isn't measured isn't done: 8 years and no progress in Indigeous adult vaccination Australian and New Zealand Journal of Public Health. 2019;In Press.
[30] Pilivishi T, Bennett N. Pneumococcal disease prevention among adults: strategies for use of pneumococcal vaccines. Vaccine 2015;33:D60–5.
[31] Remschmidt C, Harder T, Wichmann O, Bogdan C, Falkenhorst G. Effectiveness, immunogenicity and safety of 23-valent pneumococcal polysaccharide vaccine revaccinations in the elderly: a systematic review. BMC Infect Dis 2016;16:711. https://doi.org/10.1186/s12879-016-2040-y.
[32] Stacey HL, Rosen J, Peterson JT, Williams-Diaz A, Gakhar V, Sterling TM, et al. Safety and immunogenicity of 15-valent pneumococcal conjugate vaccine (PCV-15) compared to PCV-13 in healthy older adults. Human Vacc Immunother 2019;15:530–9.
[33] Thompson A, Lamberth E, Severs J, Scully I, Tarabar S, Ginis J, et al. Phase 1 trial of a 20-valent pneumococcal conjugate vaccine in healthy adults. Vaccine 2019;37:6201–7.
[34] Hurtado K, Platt H, Shekar T, Su SC, Pedley A, Acosta C, et al. A phase 2, double-blind, randomized, multicenter trial to evaluate the safety and immunogenicity of 15-valent pneumococcal conjugate vaccine (pcv15) compared to pcv13 in healthy infants. 37th Annual Meeting of the European Society for Paediatric Infectious Diseases, 2019.