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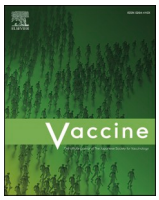

Reduction in self-reported adverse events in Australian adults after change to national immunisation schedule from polysaccharide to conjugate pneumococcal vaccine, 2016–2022

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ABSTRACT

Background: On 1 July 2020, the Australian pneumococcal immunisation program schedule changed from 23-valent pneumococcal polysaccharide vaccine (23vPPV) for ≥65 year olds to 13-valent pneumococcal conjugate vaccine (13vPCV) for ≥70 year olds as the primary dose. We compared the short-term safety in a real-world setting between November 2016 to March 2022 using AusVaxSafety, Australia's active surveillance system for self-reported adverse events following immunisation. **Methods:** Australian adults who received a pneumococcal vaccine at one of more than 300 AusVaxSafety participating immunisation providers between 1 November 2016 and 31 March 2022 were asked to report any adverse events in the seven days after vaccination. We analysed counts, proportions and odds of reporting any event, solicited events and any medical attention (proxy for serious event). We used a mixed-effect logistic regression to estimate odds ratios (aOR) adjusted for sex, age in years, Indigenous status, dose number, and concomitant vaccination, and included vaccination location and unique patient as random effects variables. **Results:** Of 70,689 responses from 91,116 encounters, adults receiving 13vPCV were 51 % less likely to report any event (aOR = 0.49; 95 % Confidence Interval (CI): 0.45–0.53) compared to those who received 23vPPV. The odds of reporting an event increased when receiving concomitant vaccination (aOR = 1.56; 95 % CI: 1.47–1.67). Indigenous status did not predict the likelihood of reporting an event (Indigenous aOR = 0.97; 95 % CI:0.79–1.20). Few participants (0.9 % (236/37,799) 23vPPV; 0.3 % (93/32,426) 13vPCV) sought medical attention. **Discussion:** These data demonstrate the change to the pneumococcal vaccine schedule did not result in more reporting of short-term adverse events following immunisation. 13vPCV has a more tolerable short-term safety profile than 23vPPV in Australian adults. Having real-world safety data of current pneumococcal vaccines provides a basis from which to monitor new, higher valency conjugate vaccines that may be added to Australia's national immunisation schedule.

1. Introduction

Pneumococcal disease (caused by *Streptococcus pneumoniae*) in Australian adults commonly presents as community acquired pneumonia and invasive pneumococcal disease (IPD), and also in less severe forms as ear (otitis media) and sinus infections.

The risk of pneumococcal disease is disproportionately high among Aboriginal and Torres Strait Islander people, hereafter referred to as Indigenous people, and people with certain underlying medical or lifestyle conditions (risk conditions) [1]. Incidence of IPD in Australia is highest in infants and toddlers (aged <5 years) and adults over 55 years [2,3]. Data published in 2015 reports pneumococcal disease accounted for 24 % of the vaccine preventable burden of disease in Australia [4]. Pneumococcus was estimated to account for more than 13 % of community acquired pneumonia cases in 2004–2006 [5]. Mortality is high, with an estimated 11–18 % of hospitalised cases aged ≥65 years dying

Abbreviations: 23vPPV, 23-valent pneumococcal polysaccharide vaccine; 13vPCV, 13-valent pneumococcal conjugate vaccine; IPD, invasive pneumococcal disease; NIP, National Immunisation Program.

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within 30 days of admission. In 2017–2019, the annual incidence rate of IPD in Australian adults aged ≥65 years was 19.6–21.8 per 100,000 population [1].

While pneumococcal disease is caused by more than 100 serotypes of *Streptococcus pneumoniae* [6], the highest burden serotypes can be effectively prevented through vaccination [7]. Pneumococcal vaccines for adults had been recommended for all adults aged ≥65 years with subsidised funding since 1997 and fully funded under the Australian National Immunisation Program (NIP) since 2008 in various schedules [8].

On 1 July 2020, the primary dose given to adults on the NIP schedule changed from the 23-valent pneumococcal polysaccharide vaccine (23vPPV) to the 13-valent pneumococcal conjugate vaccine (13vPCV). For Indigenous people ≥50 years of age and adults ≥18 years of age with a risk condition, 23vPPV was given as second and third doses [9]. The age at which all adults were eligible for a pneumococcal vaccine (13vPCV) increased to ≥70 years at the same time. The change to the NIP was due to several factors. Incidence of IPD in non-Indigenous Australians aged ≥70 years was higher compared to 65–70-year-olds who were previously covered under the NIP [10]. 13vPCV possessed superior efficacy and effectiveness compared to 23vPPV [11] which was demonstrated to provide almost no protection five years post-vaccination [12]. In addition, the serotypes of pneumococcus that were causing the greatest incidence of disease in non-Indigenous Australian adults were well covered by 13vPCV, whereas Indigenous people were at greater risk from serotypes covered in 23vPPV not in 13vPCV [13]. Extended valency conjugate vaccines (15- and 20-valent) are available as alternatives to 13vPCV, but are not currently NIP-funded.

While the schedule change to the NIP was primarily driven by the desire to ensure the best protection for those that need it, monitoring safety following schedule changes is important. Clinical trials for 23vPPV and 13vPCV reported common mild reactions in adult recipients and the Australian context provided an opportunity to compare safety profiles. In this article, we compared the short-term safety of the two pneumococcal vaccines funded for adults under the Australian NIP, assessed in a real-world setting during November 2016 to March 2022 using a large dataset of self-reported adverse events actively elicited from primary care settings across Australia.

2. Materials and methods

The study population is NIP-eligible by age Australian adults who received a pneumococcal vaccine at an AusVaxSafety participating primary health care provider (general practices and immunisation clinics) between 1 November 2016 and 31 March 2022. AusVaxSafety undertakes regular monitoring of adverse events reported in the days after vaccination through collection of survey data from individuals following routinely administered vaccines across 317 sentinel immunisation providers in all states and territories of Australia [14,15]. It has collected vaccine safety data on adult pneumococcal vaccination since 2016 [14]. Automated text messages or emails were sent 3–5 days following vaccination at a participating immunisation provider, seeking responses to a survey about any reaction following immunisation. Survey responses submitted within 7 days post vaccination encounter were included in the analysis. Participants who responded that they had experienced an adverse event received a second SMS asking if they sought medical attention and a link to a survey requesting information about the event [14].

De-identified data reporting vaccination and demographic details from each participating immunisation provider were stored on a secure data server. Using deidentified data flagged in AusVaxSafety, state and territory public health authorities are notified of any reported medically attended events following immunisation for further investigation, as per legislative requirements.

This study included Australian adult pneumococcal vaccination encounters for non-Indigenous adults aged ≥65 years and Indigenous adults ≥50 years for 23vPPV and aged ≥70 years and Indigenous adults ≥50 years for 13vPCV (Fig. 1). 23vPPV administered to Indigenous adults following the NIP schedule change in 2020 were not included in the analysis as these were likely non-primary doses. We analysed the responses of adults based on vaccine type administered: those who received 23vPPV between November 2016 and June 2020, those who received 13vPCV from July 2020 (when the NIP schedule changed [9]) to March 2022.

The primary outcomes of interest were reports of any event or medical attention at a medical practice or emergency department (a proxy for serious event) within seven days of pneumococcal vaccine administration. The comparison group comprised respondents who reported no events, and non-respondents were excluded from the analysis. The survey asked about specific events of interest (solicited event) including pain, redness or swelling at injection site, tiredness, fever, headache, rash, rigors, diarrhoea and/or vomiting, seizure or other symptoms. An absence of an event in an otherwise completed survey was treated as no event reported. If demographic data were missing, the observation was excluded in the relevant stratified analysis. Other missing data were assumed “not reported”.

We analysed counts, proportions and odds of reporting any event, solicited events and any medical attention (proxy for serious event). The characteristics for each vaccine type were compared to participants who did not experience an event using chi square tests, or Fisher exact tests where cell counts were less than five. We calculated unadjusted odds ratios (OR) and used a mixed-effect logistic regression to estimate adjusted odds ratios (aOR). Confounding variables were selected *a priori*. We adjusted for sex, age (in years as a numeric variable), Indigenous status, dose number and concomitant vaccination. To account for possible non-independence, we included practice for where the encounter took place and unique patient as random effects variables in the mixed model. Additional analysis of odds of reporting events or seeking medical attention after vaccination based on concomitant status (receiving multiple vaccines at the same encounter) was conducted using factorial logistic regression. Statistical significance was set at <0.05. All analysis was conducted in Stata statistical software version 14 [16]. This study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

2.1. Ethics

AusVaxSafety operates under human research ethical approval 2019/ETH06075 obtained from the Sydney Children’s Hospital Network Ethics Committee. Participant consent was determined on an opt-out basis as approved under the ethics application. Participants may also choose to revoke consent at any stage of the survey.

3. Results

3.1. Study cohort

There were 91,116 pneumococcal vaccine encounters between 1 November 2016 and 31 March 2022, identified from 317 immunisation providers. Three encounters were excluded due to listing both vaccine types for the same vaccination encounter, and an additional 16 observations were excluded for being duplicate vaccine encounters. 70,689 participants responded to the survey within 7 days of the vaccination encounter and were eligible for inclusion in the analysis (77.6 %) (Table 1). Of the 70,689 participants, 2756 (3.9 %) received more than one pneumococcal vaccine during the whole study period, and 67,933 (96.1 %) were participants who received a single pneumococcal vaccine in the period. See supplementary fig. 1.

Of 70,689 participants, 37,796 (53.5 %) received 23vPPV and 32,893 (46.5 %) received 13vPCV (Table 1). Cohorts were similar in terms of sex and Indigenous status (23vPPCV: 53.0 % female; 2.3 %

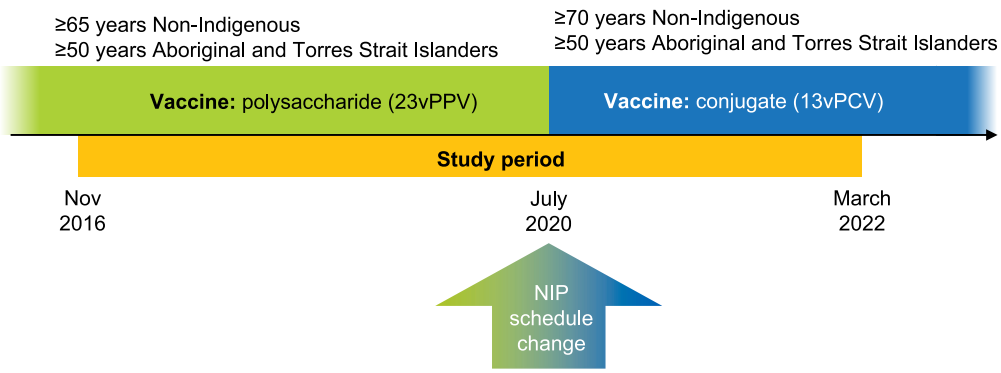

Fig. 1. Study period and participants.

Indigenous, 13vPCV: 55.2 % female; 1.9 % Indigenous). Median [interquartile range] age was lower in the 23vPPV cohort (23vPPV: 68 years [66–72]; 13vPCV: 74 years, [71–78]) due to the difference in vaccine-eligible age for adult pneumococcal vaccination under the NIP schedules. A greater proportion of participants who received 23vPPV received at least one concomitant vaccine. The most commonly received concomitant vaccine for both groups was influenza; Zoster was the second most received concomitant vaccine.

3.2. Outcomes

3.2.1. Adverse events following either pneumococcal vaccine

3.2.1.1. Any adverse event. Of the study population, 11.3 % (7967) of participants reported an adverse event following immunisation. Of those reporting any adverse event, 65.0 % (5177) were female, 2.3 % (154) were Indigenous, and 53.4 % (4252) had received a concomitant vaccine in addition to the pneumococcal vaccine (Table 1). The proportion of Indigenous people, with respect to non-Indigenous people, reporting any event was similar between groups (12.1 % vs 11.0 %). Adverse events were more commonly reported by participants who received concomitant vaccination compared to those who received only a pneumococcal vaccine of either type (14.4 % vs 9.0 %).

3.2.1.2. Solicited adverse events:. The most commonly reported solicited adverse event by recipients of either vaccine type was pain, redness or swelling at the injection site.

3.2.1.3. Medical attention:. Seeking medical attention for an event, a proxy for serious adverse events, was reported for 0.6 % (419) of all participants. Of these, 68.5 % (287) were female, 3.1 % [13] were Indigenous, and 57.3 % (240) had received a concomitant vaccine (Table 3). Indigenous people receiving either pneumococcal vaccine reported seeking medical attention more than non-Indigenous people (1.1 % vs 0.6 %). Seeking medical attention was more commonly reported by individuals who received concomitant vaccine compared to those who received only a pneumococcal vaccine (0.8 % vs 0.4 %).

3.2.2. Adverse events reported by pneumococcal vaccine type

3.2.2.1. Any adverse event. Adjusting for sex, Indigenous status, age, concomitant vaccination, practice and unique patient, participants receiving 13vPCV were 51 % less likely to report any event (aOR = 0.49; 95 % Confidence Interval (CI): 0.45–0.53) compared to participants who received 23vPPV. The mixed effects model (see supplementary table 1) showed that the odds of reporting an adverse event increased for individuals receiving concomitant vaccination (aOR = 1.56; 95 % CI: 1.47–1.67;); and decreased for men compared to women (aOR = 0.55; 95 % CI: 0.52–0.59). For each one year increase in age, odds of reporting any adverse event decreased by 0.8 % (aOR = 0.992; 95 % CI: 0.987–0.992; $p < 0.01$). Indigenous status did not predict the likelihood of reporting an adverse event (Indigenous aOR = 0.97; 95 % CI:0.79–1.20).

3.2.2.2. Solicited adverse events. For each type of solicited event recipients of 23vPPV were two to four times more likely to report any event compared to recipients of 13vPCV when adjusting for other variables (Table 2). Rigors and rash were almost four times as commonly reported in 23vPPV recipients than 13vPCV recipients. There was no statistically significant relationship between vaccine type and reporting gastrointestinal symptoms or seizure.

3.2.2.3. Medical attention. Absolute numbers of individuals seeking medical attention were low (326 recipients of 23vPPV (0.9 %) and 93 recipients of 13vPCV (0.3 %)) (Table 2). The model showed recipients of 13vPCV were 61 % less likely to seek medical attention than recipients of 23vPPV (aOR = 0.39; 95 % CI: 0.30–0.52). Consistent with reporting of any adverse event, participants were more likely to report seeking medical attention if they received a concomitant vaccination than if they received either pneumococcal vaccination only (aOR = 1.56, 95 % CI: 1.27–1.92) (Table 4), but men were less likely than women (aOR = 0.54, 95 % CI: 0.44–0.67). Indigenous status and age did not predict the likelihood of reporting an adverse event (Indigenous aOR = 1.65; 95 % CI: 0.89–3.06; age aOR = 1.00; 95 % CI: 0.98–1.01).

3.2.2.4. Concomitant vaccination:. Additional analysis was done to examine whether receiving multiple vaccinations at a single encounter increased the odds of reporting an adverse event or requiring medical attention (Table 4). While 51 % of participants received another vaccine at the time the polysaccharide vaccine was administered, only 31 % of participants who received the newer conjugate vaccine also received another vaccine. Results showed that having at least one additional vaccine at an a pneumococcal vaccine encounter (either type) increased the odds of reporting an adverse event. Recipients of 13vPCV only had the lowest odds of reporting any event, whereas individuals receiving 23vPPV with any other vaccine had the highest odds of reporting any event or requiring medical attention. The adjusted odds ratio of reporting any event when receiving a concomitant vaccine is 1.8 compared to only receiving a pneumococcal vaccine (of either type). The adjusted odds ratio of reporting a serious event indicated by reporting seeking medical attention in combination with another vaccine being administered was 1.6 compared with only receiving a pneumococcal vaccine of either type.

4. Discussion

Analysis of self-reported adverse events following pneumococcal vaccination by NIP-eligible by age Australian adults, before and after the

Table 1
Overview of participants receiving NIP-funded pneumococcal vaccination by vaccine type in AusVaxSafety vaccine safety surveillance, 1 November 2016 to 31 March 2022.

	Total pneumococcal vaccines (1 November 2016 to 31 March 2022)	**23vPPV** (1 November 2016 to 30 June 2020)	**13vPCV** (1 July 2020 to 31 March 2022)	**p-value**[a]
Encounters	91,113	49,582 (54.4 %)	38,701 (45.6 %)	
Participants	70,689	37,796 / 70,689 (53.5 %)	32,893 / 70,689 (46.5 %)	
Demographics				
Male [b]	32,497 / 70,649 (46.00 %)	17,760 / 37,768 (47.02 %)	14,737 / 32,881 (44.82 %)	<0.001
Female	38,152 / 70,649 (54.00 %)	20,008 / 37,768 (52.98 %)	18,144 / 32,881 (55.18 %)	<0.001
Aboriginal or Torres Strait Islander [c]	1272 / 61,039 (2.08 %)	714 / 31,495 (2.27 %)	558 / 29,544 (1.89 %)	<0.001
Non-Aboriginal or Torres Strait Islander	59,767 / 61,039 (97.92 %)	30,781 / 31,495 (97.73 %)	28,986 / 29,544 (98.11 %)	<0.001
Age, median [IQR], y	71 [68–78]	68 [66–72]	74 [71–78]	<0.001
Age group, years				
50–64[d]	725 / 70,689 (1.03 %)	440 / 37,796 (1.16 %)	285 / 32,893 (0.87 %)	
65–69[e]	21,218 / 70,689 (30.01 %)	21,154 / 37,796 (55.96 %)	67 / 32,893 (0.20 %)	
70–74	26,967 / 70,689 (38.15 %)	10,383 / 37,796 (27.47 %)	16,589 / 32,893 (50.41 %)	
75–79	13,233 / 70,689 (18.72 %)	3919 / 37,796 (10.37 %)	9319 / 32,893 (28.32 %)	
80–84	57,328 / 70,689 (8.11 %)	1330 / 37,796 (3.52 %)	4401 / 32,893 (13.37 %)	
85–89	2097 / 70,689 (2.97 %)	432 / 37,796 (1.14 %)	1665 / 32,893 (5.06 %)	
≥90	721 / 70,689 (1.02 %)	141 / 37,796 (0.37 %)	580 / 32,893 (1.76 %)	
Receipt of ≥1 concomitant vaccine, No. / Total No. (%)[f]				
Any	29,443 / 70,689 (41.7 %)	19,248/ 37,796 (50.9 %)	10,195 / 32,893 (31.0 %)	
Influenza	23,317 / 70,689 (33.0 %)	17,201 / 37,769 (45.5 %)	6116 / 32,893 (19.0 %)	
Zoster	4362 / 70,689 (6.2 %)	1422 / 37,796 (3.8 %)	2940 / 32,893 (8.9 %)	

23vPPV: 23-valent pneumococcal polysaccharide vaccine, 13vPCV: 13-valent pneumococcal conjugate vaccine,
NIP: National Immunisation Program, IQR: Interquartile range, No: number.
23vPPV administered after 1 July 2020 are not included in these data.
[a] *p*-value calculated using Chi-squared test to calculate difference between the two vaccine groups.
[b] Sex data were available for 70,649 participants.
[c] Indigenous status data were available for 61,039 participants.
[d] Age groups combined as only Indigenous people eligible for NIP-funded pneumococcal vaccination in this age group.
[e] Only Indigenous people eligible for NIP-funded 13vPCV in this age group.
[f] Concomitant vaccines may have been given alone with a pneumococcal vaccine or in combination with pneumococcal and another vaccine.

Table 2
Odds ratios of adult recipients of 13vPCV reporting any event, seeking medical attention, or specified solicited event following immunisation, compared to receiving 23vPCV, AusVaxSafety data 1 November 2016–31 March 2022.

Type of adverse event	**23vPPV encounters**	**13vPPV encounters**	**Odds ratio (OR) 13vPCv vs 23vPPV (Ref)**	
			Unadjusted OR (95 % CI)	**Adjusted OR (95 % CI)**
Any	5495/ 37,796 (14.5 %)	2473/ 32,893 (7.5 %)	0.48 (0.45–0.50)	0.49 (0.45–0.53)
Medical attention	326/37,035 (0.9 %)	93/32,413 (0.3 %)	0.32 (0.26–0.41)	0.39 (0.30–0.52)
Solicited events				
Pain or redness/ swelling at injection site	2265/ 34,989 (6.5 %)	1007/ 29,173 (3.5 %)	0.52 (0.48–0.56)	0.51 (0.47–0.56)
Fever	698/34,994 (1.99 %)	181/31,789 (0.57 %)	0.28 (0.24–0.33)	0.34 (0.27–0.41)
Rash	293/34,994 (0.8 %)	77/31,789 (0.2 %)	0.29 (0.22–0.37)	0.28 (0.21–0.38)
Rigors	175/34,994 (0.50 %)	32/31,789 (0.1 %)	0.20 (0.14–0.29)	0.25 (0.17–0.36)
Headache	873/34,994 (2.5 %)	369/31,789 (1.2 %)	0.46 (0.41–0.52)	0.54 (0.47–0.61)
Gastrointestinal symptoms	16/34,994 (0.05 %)	5/31,789 (0.02 %)	0.34 (0.13–0.94)	0.44 (0.16–1.23)
Seizure	2/34,994 (0.01 %)	1/31,789 (<0.01 %)	0.55 (0.05–6.07)	0.55 (0.05–6.26)
Fatigue	1287/ 34,994 (3.7 %)	569/31,789 (1.8 %)	0.48 (0.43–0.53)	0.55 (0.50–0.62)
Other symptoms[a]	1136/ 34,994 (3.3 %)	492/31,789 (1.6 %)	0.47 (0.42–0.52)	0.53 (0.47–0.59)

Denominators are calculated for each question and may vary. Adjusting for sex, Indigenous status, age in years, concomitant vaccination, practice and unique patient.
23vPPV: 23-valent pneumococcal polysaccharide vaccine, 13vPCV: 13-valent pneumococcal conjugate vaccine,
OR: odds ratio, CI: 95 % confidence interval.
[a] Other includes the solicited adverse events of irritability, fainting, as well as unsolicited adverse events. Common unsolicited adverse events included nausea, myalgia and cold symptoms, such as sore throat and runny nose.

NIP schedule changed from a polysaccharide vaccine to a conjugate vaccine, found that adjusting for covariates, recipients of the conjugate vaccine were consistently less likely to report any adverse event or seek medical attention. Furthermore, recipients of the polysaccharide vaccine having another vaccine at the same time had the highest odds of reporting an event. Even receiving the 23vPPV alone resulted in higher odds of reporting an event compared to receiving 13vPCV and another vaccine concomitantly.

Due to the age group recommendations for non-Indigenous recipients changing from ≥65 years for 23vPPV to ≥70 years for 13vPCV, we included age at vaccination in years in the model to adjust for confounding [17]. Our results align with previous evidence from both clinical trials and post-licensure safety studies suggesting younger adult recipients of 23vPPV are more likely to experience an adverse event following immunisation than older recipients of the same vaccine [18,19].

Males were approximately half as likely as women to report any event or to seek medical attention following immunisation. This is consistent with the Vaccine Adverse Event Reporting System (VAERS) post-market surveillance of 23vPPV administration from 1990 to 2013

Table 3
Summary of participants by event report type from adult recipients of pneumococcal vaccine, AusVaxSafety data 1 November 2016–31 March 2022.

	All pneumococcal vaccines			23vPPV			13vPCV		
	No event	Any event	Medical attention	No event	Any event	Medical attention	No event	Any event	Medical attention
Demographics									
Male	29,714 (91.4 %)	2783 (8.6 %)	130/32,001 (0.4 %)	15,752 (88.7 %)	2008 (11.3 %)	102/17,427 (0.6 %)	13,957 (94.8 %)	773 (5.3 %)	28/14,576 (0.2 %)
Female	32,975 (86.4 %)	5177 (13.6 %)	287/37,391 (0.8 %)	16,526 (82.6 %)	3482 (17.4 %)	223/19,579 (1.1 %)	16,444 (90.7 %)	1695 (9.3 %)	64/17,814 (0.4 %)
Aboriginal or Torres Strait Islander	1118 (87.9 %)	154 (12.1 %)	NP (1.1 %)	608 (85.2 %)	106 (14.6 %)	NP (1.5 %)	510 (91.4 %)	48 (8.6 %)	NP (0.6 %)
Non-Aboriginal or Torres Strait Islander	53,181 (89.0 %)	6601 (11.0 %)	346/58,757 (0.6 %)	26,334 (85.5 %)	4450 (14.5 %)	265/30,180 (0.9 %)	26,839 (92.6 %)	2149 (7.4 %)	81/28,577 (0.3 %)
Age group (years)									
50–64	635 (87.6 %)	90 (12.4 %)	NP (1.1 %)	374 (85.0 %)	66 (15.0 %)	NP (1.8 %)	261 (91.6 %)	24 (8.4 %)	NP (0.7 %)
54–69	18,162 (85.6 %)	3058 (14.4 %)	177/20,843 (0.9 %)	18,102 (85.6 %)	3051 (14.4 %)	177/20,778 (0.9 %)	NP (89.6 %)	NP (10.5 %)	0/65 (0.0 %)
70–74	23,971 (88.9 %)	2995 (11.1 %)	148/26,505 (0.6 %)	8777 (84.5 %)	1606 (15.5 %)	98/10,151 (1.0 %)	15,194 (91.6 %)	1389 (8.4 %)	50/16,354 (0.3 %)
75–79	12,037 (91.0 %)	1198 (9.1 %)	58/13,017 (0.5 %)	3366 (85.9 %)	553 (14.1 %)	33/3827 (0.9 %)	8671 (93.1 %)	645 (6.9 %)	25/9190 (0.3 %)
80–84	5297 (92.5 %)	431 (7.5 %)	18/5616 (0.3 %)	1171 (88.1 %)	159 (12.0 %)	9/1296 (0.7 %)	4126 (93.8 %)	272 (6.2 %)	9/4320 (0.2 %)
85–90	1952 (93.1 %)	145 (6.9 %)	NP (0.3 %)	386 (89.4 %)	46 (10.7 %)	NP (0.5 %)	1566 (94.1 %)	99 (6.0 %)	NP (0.2 %)
90+	672 (93.2 %)	49 (6.8 %)	NP (0.6 %)	127 (90.1 %)	14 (9.9 %)	NP (0.7 %)	545 (94.0 %)	35 (6.0 %)	NP (0.5 %)
Concomitant vaccine									
Any	25,191 (85.6 %)	4252 (14.4 %)	240/28,851 (0.8 %)	15,956 (82.9 %)	3292 (17.1 %)	203/18,811 (1.1 %)	9235 (90.6 %)	960 (9.4 %)	37/10,040 (0.4 %)
Influenza	19,725 (84.6 %)	3592 (15.4 %)	209/22,861 (0.9 %)	14,161 (82.3 %)	3040 (17.7 %)	193/16,830 (1.1 %)	5564 (91.0 %)	552 (9.0 %)	21/6065 (0.4 %)
Zoster	3834 (87.9 %)	528 (12.1 %)	28/4300 (0.7 %)	1210 (85.1 %)	212 (14.9 %)	13/1385 (0.9 %)	2624 (89.3 %)	316 (10.7 %)	15/2917 (0.5 %)

note: denominator for serious events will be different to sum of no event and any event as not all participants completed the question. Totals may not add to 100 % due to rounding.
NP: not published due to low cell counts.

Table 4
Odds ratios of Australian adults reporting any event or seeking medical attention following immunisation with pneumococcal vaccines according to concomitant status, compared to receiving 13vPCV only, AusVaxSafety data 1 November 2016–31 March 2022.

Outcome	Vaccine/s received	Unadjusted OR (95 % CI)	Adjusted OR (95 % CI)
Any event	13vPCV alone	1 (reference)	1 (reference)
	13vPCV + other vaccine	1.45 (1.34–1.58)	1.46 (1.31–1.62)
	23vPPV alone	1.88 (1.76–2.01)	1.92 (1.75–2.12)
	23vPPV + other vaccine	2.87 (2.67–3.05)	3.12 (2.81–3.46)
Medical attention	13vPCV alone	1 (reference)	1 (reference)
	13vPCV + other vaccine	1.40 (0.94–2.08)	1.27 (0.82–1.96)
	23vPPV alone	2.50 (1.85–3.38)	2.24 (1.59–3.16)
	23vPPV + other vaccine	4.01 (3.03–5.30)	3.72 (2.68–5.17)

23vPPV: 23-valent pneumococcal polysaccharide vaccine, 13vPCV: 13-valent pneumococcal conjugate vaccine, OR: odds ratio, CI: confidence interval.

in the USA, where 63 % of adverse events were reported by females [20].

Our results indicate that when administered alone or concomitantly, participants receiving 13vPCV were less likely to report an adverse event compared to participants receiving 23vPPV. This contrasts previous studies looking at similar outcomes that found no difference between groups receiving either pneumococcal vaccine [21], either vaccine concomitantly with an influenza vaccine [22] or receiving 13vPCV administered alone or concomitantly [23]. Others found recipients of concomitant 13vPCV with an influenza vaccine reported adverse events more frequently than receiving it alone [24], which mirrors our study's results. Our results suggest that the difference in reporting of adverse events (any event and those requiring medical attention) is due to the reactogenicity of the polysaccharide vaccine rather than administering multiple vaccines at the same encounter (Table 4). Analysis of adverse events reported after administration of 23vPPV as second or third doses may provide further explanation.

There have been few clinical studies that assess safety of conjugate pneumococcal vaccines in adults aged ≥65 years, and fewer studies assessing post-market safety. In our study, the proportion of participants reporting any adverse event or medical attention following receipt of 13vPCV was low compared to clinical trials in similar populations. Clinical trials demonstrate adverse events were more common in adults 60–64 years receiving a dose of 13vPCV compared to adults receiving their first dose of 23vPPV [9]. Furthermore, reporting an event during clinical trials was more common after a repeat dose of 23vPPV than after a repeat dose of 13vPCV in adults [25]. While we were unable to assess the same effect due to data limitations, in our study, participants who received 23vPPV were generally twice as likely to report an event than those who received 13vPCV. In one clinical trial, at least half of 23vPPV recipients experienced pain at the injection site after the first dose, and swelling and redness were present in approximately 20 % of recipients [26], much higher reporting rates than from the AusVaxSafety active

surveillance of 6.5 %, due to the methodological differences between the two study designs.

There are limitations inherent in the AusVaxSafety active surveillance system. For example, information provided by participants is not verified by medical practitioners and misclassification of event type (by recipient) and of vaccine type (by practice) is possible. Events captured by AusVaxSafety are those reported after vaccination; causality has not been assessed. Results, therefore, may overestimate true rates of events associated with vaccination. Though AusVaxSafety sites are geographically spread across Australia to provide a representative sample of the Australian population, because AusVaxSafety is a sentinel surveillance system, results may not be representative of all patients who receive pneumococcal vaccines.

Self-selection bias was likely present. While more than three-quarters of those vaccinated at an AusVaxSafety participating site responded, 22.4 % elected not to respond. Participants required access to a mobile phone with internet data or access to email, and the survey was only available in English. Both of these factors may have limited responses from some sub-populations. Self-selection may have skewed the results in favour of reporting higher grade events, i.e. those with mild events may have been less likely to respond than those who experienced a more serious adverse event. Conversely, people who experienced a serious event may have been unable to respond. Despite this, reports of medical attention were low, and reports of solicited events were lower than reported in the clinical trials.

We were unable to draw any conclusions about a significant relationship between vaccine type and the adverse events seizure and gastrointestinal symptoms due to small numbers of reports. Though it is well reported that revaccination with subsequent doses of 23vPPV is associated with a higher rate of reporting adverse events following immunisation [27], we were unable to adjust for 23vPPV dose number as our data did not allow us to ascertain which participants receiving 13vPCV had received a prior dose of 23vPPV.

Despite these limitations, these data are useful for demonstrating that the change to the adult pneumococcal vaccine schedule has not resulted in higher reporting of adverse events following immunisation. Our results show 13vPCV has a more tolerable short term safety profile than 23vPPV. Our study was able to compare real-world safety before and after the adult pneumococcal vaccine schedule change, adding to the limited evidence available.

5. Conclusion

AusVaxSafety data are useful post-marketing safety data for quickly and clearly demonstrating safety of vaccines to the public and providers. Having safety data of individual current pneumococcal vaccines provides a strong basis from which to monitor new, higher valency conjugate pneumococcal vaccines that may be added to the Australian national immunisation schedule.

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CRediT authorship contribution statement

Zoë Croker: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Formal analysis, Data curation. **Angus McLure:** Writing – review & editing, Supervision, Methodology. **Alexis Pillsbury:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Lucy Deng:** Writing – review & editing, Supervision, Project administration, Methodology. **Helen Quinn:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2025.127432.

Data availability

The data that has been used is confidential.

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