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Persistence of immunity to conjugate and polysaccharide pneumococcal vaccines in frail, hospitalised older adults in long-term follow up

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ABSTRACT

Background: Data on long-term antibody responses to pneumococcal vaccines in the elderly, especially the frail elderly at greatest risk of severe disease, are limited. We followed up participants in a randomised trial of the immunogenicity of 23-valent polysaccharide vaccine (23vPPV) and 7 valent pneumococcal conjugate vaccines (PCV7) in hospitalised older adults.

Methods: We measured antibody to vaccine serotypes by standardised enzyme-linked immunosorbent assay (ELISA) and opsonophagocytic (OPA) assays. A follow up study was conducted six years after vaccination with 23vPPV alone or with PCV7 followed by 23vPPV six months later.

Results: Of 215 surviving trial participants, 136 (63%) completed follow up; 62 received 23vPPV and 74 received PCV7 + 23vPPV. There was no significant difference in death and readmission between arms. Antibody levels by ELISA and OPA did not differ significantly between the two study arms at 72 months post-vaccination. ELISA and OPA antibody remained higher than baseline except for OPA antibody to 4, 6A, 6B, 9v, 19F and 23F, including in subjects with undetectable immunity at baseline.

Discussion: While ELISA responses in both study arms remained high 6 years post-vaccination, considerable waning was observed by OPA in both study arms, which should be considered given the current single-dose recommendation in Australia. Further research is needed to inform pneumococcal vaccine recommendations in people over the age of 65.

1. Introduction

Infection with *Streptococcus pneumoniae* causes invasive pneumococcal disease (IPD) and is the most common pathogen identified in cases of community-acquired pneumonia (CAP) [1,2]. Adults over the age of 65 are at increased risk of severe disease and death due to IPD and CAP, particularly if they have other underlying health conditions [1,3–7]. Given that the proportion of the population over 65 years old is increasing, developing an effective pneumococcal vaccination strategy is a matter of public health importance [8].

In Australia and the United Kingdom, adults aged 65 and older without high risk medical conditions are recommended to receive a single dose of 23-valent polysaccharide pneumococcal vaccine [9,10]. Previously, a five year booster dose was recommended for this group in Australia, but this was removed from the recommendations in 2011 [11]. Due to the greater immunogenicity and efficacy of pneumococcal conjugate vaccines, including proven efficacy against adult community acquired pneumonia [12], some countries, such as the United States, recommend either PCV alone or a combination of PCV followed by 23vPPV for adults over 65 [12–15].

We previously reported the immunogenicity of 23-valent polysaccharide vaccine (23vPPV) and 7 valent pneumococcal conjugate vaccines (PCV) in hospitalised older adults and showed that there was no clear advantage of a single dose of 7-valent PCV over 23vPPV in hospitalized older people in Australia 6 months after vaccination [16]. However, while waning of OPA antibodies after 12 months was observed among individuals that received only 23vPPV, antibody levels increased after 12 months in individuals that received PCV7 followed by 23vPPV, suggesting a boosting effect of a combined schedule [16].

There are limited data on the long-term immunogenicity of pneumococcal vaccines in older populations. Studies have demonstrated that antibody levels remain above pre-vaccination levels

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for more than five years after vaccination with 23vPPV [17–20]. Vaccination with PCV also elicits increased antibody levels that persist for at least two years in older adults [21,22]. In this paper, we present the results of a six-year follow up study of our previous clinical trial conducted among hospitalized older adults [16]. We aimed to determine the persistence of immunity in older adults that received either 23vPPV alone or PCV7 followed 6 months later by 23vPPV. This is the first study, to our knowledge, of pneumococcal immunity beyond five years in frail older adults.

2. Methods

2.1. Study design and recruitment

We conducted a six-year follow up study of an open-label, randomized, controlled clinical trial to compare the immunogenicity of PCV7 and 23vPPV in unvaccinated, hospitalised older adults that was conducted between May 2005 and February 2008 [16]. Inclusion criteria for adults admitted to geriatric, cardiology, rheumatology, or orthopaedic wards at the participating hospital were being 60 years of age or older and no previous history of pneumococcal vaccination. Self-reported vaccination history was validated by each participant's physician. Patients were excluded if they were not stable enough to provide informed consent, or consent could not be obtained by the patient's legal guardian. Participants were randomized to receive a single dose of either 23vPPV (control – standard immunisation recommendation at the time) or PCV7 (intervention). Participants that received PCV7 were given a dose of 23vPPV six months later, because 23vPPV was the recommended vaccine on the National Immunisation Schedule. Antibody levels were measured by ELISA and OPA at baseline and 6- and 12-months post-vaccination as described below.

Methods of recruitment, consent, and randomization for the initial trial have been published previously [16]. Fig. 1 shows the Consort diagram for the initial trial and long-term follow up. To recruit patients for the six years follow up study, we first reviewed hospital records to identify any deaths in the initial trial subjects. Excluding deceased subjects, we contacted their last known general practitioner (GP) to review vital status, vaccinations received, and any medical presentations not resulting in hospitalisation. If their GP believed he or she was still alive, we provided patient information leaflets and a consent form for the GP to provide to their patient. Trial staff followed up with patients that did not respond to the letter by telephone. We obtained consent from either the patient or their guardian prior to data collection. We visited participants in their homes to conduct interviews and collect serum samples.

2.2. Outcomes and data collection

The main outcomes of this follow up study were maintenance or change in pneumococcal antibody levels and functional antibody status 5 years after the last follow up (12 months), which was 6 years after baseline vaccination. The primary endpoint was serological response to vaccines as measured by ELISA and OPA.

Serum samples were collected from participants 60 months after the 12 months follow up (72 months from baseline) visit and stored at −80 °C until tested. Serology testing was conducted

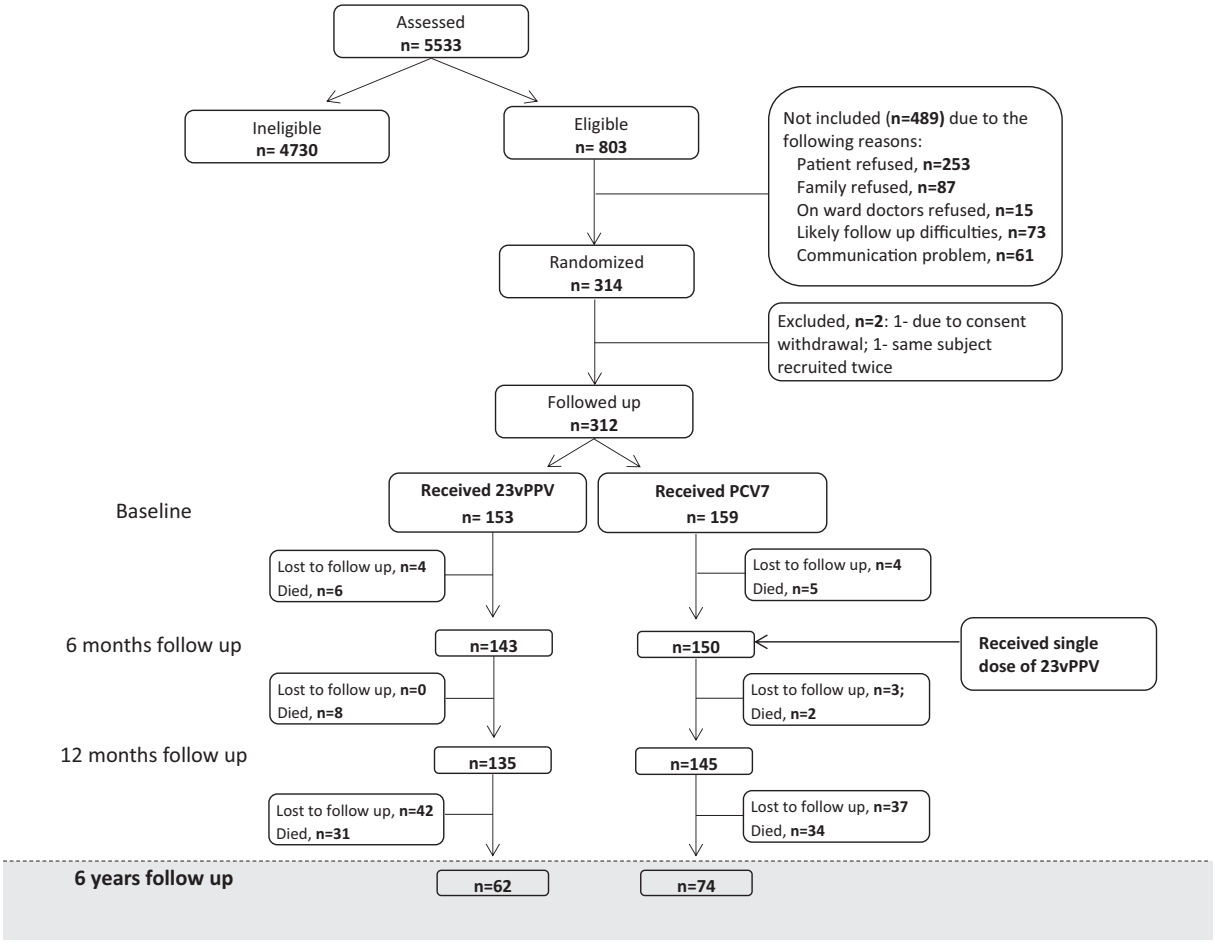

Fig. 1. CONSORT diagram of recruitment for the initial and follow up study.

at the laboratories of Pfizer Vaccine Research (Pearl River, NY), or at the Pfizer-contract laboratory PPD (Richmond, VA). To determine IgG antibody concentrations, anti-pneumococcal polysaccharide antibodies against serotypes 3, 4, 6A, 6B, 9V, 14, 18C, 19A, 19F and 23F were enumerated by ELISA using C-PS and 22F serotype capsular PS absorption. This method has been described in detail previously [23]. Opsonic activities were measured using opsonophagocytic assay (OPA) for serotypes 4, 6A, 6B, 9V, 14, 18C, 19A, 19F and 23F. Details of the OPA methods used in this study have been published previously [24]. The lower limit of detection was a titre equal to 1:8. There were inadequate volumes of sera to test for serotype 3.

Secondary outcomes included survival and hospital readmission rates. We measured frailty as a predictor, using a modified Frailty index (FI) [16]. The Frailty Index includes a list of 40 items, most of which are comorbidities. For each comorbidity present, the participant receives one point. The total frailty score is the total number of comorbidities, with a minimum score of 0 and a maximum score of 40. A score of 1–10 was considered low frailty, 11–15 was considered morderate frailty, and 16–24 was considered severe frailty.

2.3. Data analysis

Details on the sample size calculations for the initial clinical trial have been published previously [16]. We calculated geometric means of antibody concentrations (GMC) of ELISA and geometric mean titers (GMT) of OPA for each treatment group for each of the 7 pneumococcal serotypes common to both vaccines (4, 6B, 9V, 14, 18C, 19F, and 23F) as well as serotypes 3 (ELISA only), 6A, and 19A, 60 months (5 years) after the last follow up visit (12 months post-vaccination), corresponding to 72 months from baseline. We constructed 95% confidence intervals by back transformation of the confidence intervals for the mean of the log transformed assay results computed using the Student *t* distribution. To compare geometric mean concentrations and geometric mean titres between the two study arms, we used unpaired 2-tailed *t*-tests. P-values for these tests were adjusted for multiple comparisons using the Sidak step down method [25]. We used *t*-test and Chi-square tests to compare patient characteristics between the two study arms. Statistical analysis and figure preparation were done using Stata version 14 [26]. We used unpaired 2-tailed *t*-tests to compare antibody GMC and GMT between individuals that were classed as low frailty versus moderate/high frailty at the follow up visit.

2.4. Ethics statement

The present study was approved by the Western Sydney Local Health Network's Human Research Ethics Committee (approval number: *HREC2010/12/4.17(3257) AU RED HREC/10/WMEAD/239*). This trial was registered with the Australian New Zealand Clinical Trials registry (Trial ID: ACTRN12613001244796) in November 2013, and the initial trial was registered in July 2007 (ACTRN12607000387426).

3. Results

Of the 280 participants that completed the 12 months follow up in the initial study, 136 (49%) completed the subsequent six years follow up. Thirty-six (13%) were lost to follow up, 43 (15%) declined to participate, and 65 (23%) died between the 12 months follow up in the initial trial and the 6 years follow up visit. Excluding deceased subjects, the response rate was 63% (136/215). Of the subjects that completed the 6 years follow up, 62 received 23vPPV and 74 received PCV7 followed by 23vPPV. Participant characteristics at 6 years follow up are summarized in Table 1. Nearly a third of all participants were moderately or severely frail, as measured by FI. There were no significant differences between the two vaccine groups, including in deaths between baseline and follow up.

Table 1
Comparison of patients' characteristics at 6 years follow up by study arm (n = 136).

Patients' characteristics	*Vaccine groups*		
	23vPPV (n = 62)	PCV7-23vPPV (n = 74)	p-value
Age			
Mean	71.00	71.08	0.94[1]
SD	6.48	6.04	
Median	69	70	
Sex			
Male, frequency (%)	31 (50.0%)	35 (47.3%)	0.75[2]
Female	31 (50.0%)	39 (52.7%)	
Frailty index			
Low (1–10)	47 (75.8%)	50 (67.6%)	0.81[1]
Moderate (11–15)	8 (12.9%)	17 (23.0%)	
Severe (16–24)	7 (11.3%)	7 (9.5%)	
Deaths between baseline and 6 years follow up	47 (30.7%)[3]	42 (26.4%)[4]	0.40[2]
At least one readmission between baseline and follow up	44 (71.0%)	57 (77.0%)	0.42[2]

[1] Estimated using student's *t*-test.
[2] Estimated using Pearson's chi-square test.
[3] Sample size at baseline was 153.
[4] Sample size at baseline was 159.

3.1. IgG antibody levels measured by ELISA

Table 2 shows geometric mean concentrations (GMC) of IgG antibody measured by ELISA 60 months after the final 12 months follow up visit in the initial study (72 months from baseline). Antibody concentrations from previous time points have been published previously [16]. There were no significant differences between trial arms.

Fig. 2 illustrates the changes in GMC for both study arms between baseline and the 72 months follow up visit. At the 72 months follow up visit, antibody levels in both study arms were still greater than baseline for all tested serotypes.

GMC increased slightly between the 12 months and 72 months follow up for serotypes 3, 4, 6A, 6B, 9V, 14, 18C, 19A, 19F, 23F in the PPV arm, and for serotypes other than 4, 18C, 19A, and 19F in the PCV7-PPV arm.

Table 2
Comparison of 23v PPV and PCV7-23vPPV for GMC (μg/mL) measured by ELISA at 72 months from baseline.

Serotype	*GMC (95% CI) at 6 years follow up*		
	23vPPV (n = 62)	PCV7-23vPPV (n = 75)	p-value
3	1.33 (0.98–1.80)	0.81 (0.61–1.08)	0.33
4	1.49 (1.00–2.21)	1.25 (0.88–1.77)	0.99
6A	3.47 (2.74–4.41)	3.53 (2.76–4.52)	0.99
6B	4.68 (3.61–6.06)	4.06 (2.96–5.57)	0.99
9V	4.55 (3.52–5.89)	4.65 (3.43–6.32)	0.99
14	13.80 (9.69–19.65)	11.44 (7.86–16.64)	0.99
18C	6.33 (4.82–8.30)	4.38 (3.24–5.93)	0.75
19A	9.85 (7.75–12.53)	7.91 (6.04–10.37)	0.98
19F	3.98 (2.76–5.73)	3.46 (2.45–4.86)	0.99
23F	4.28 (3.22–5.69)	4.60 (3.30–6.40)	0.99

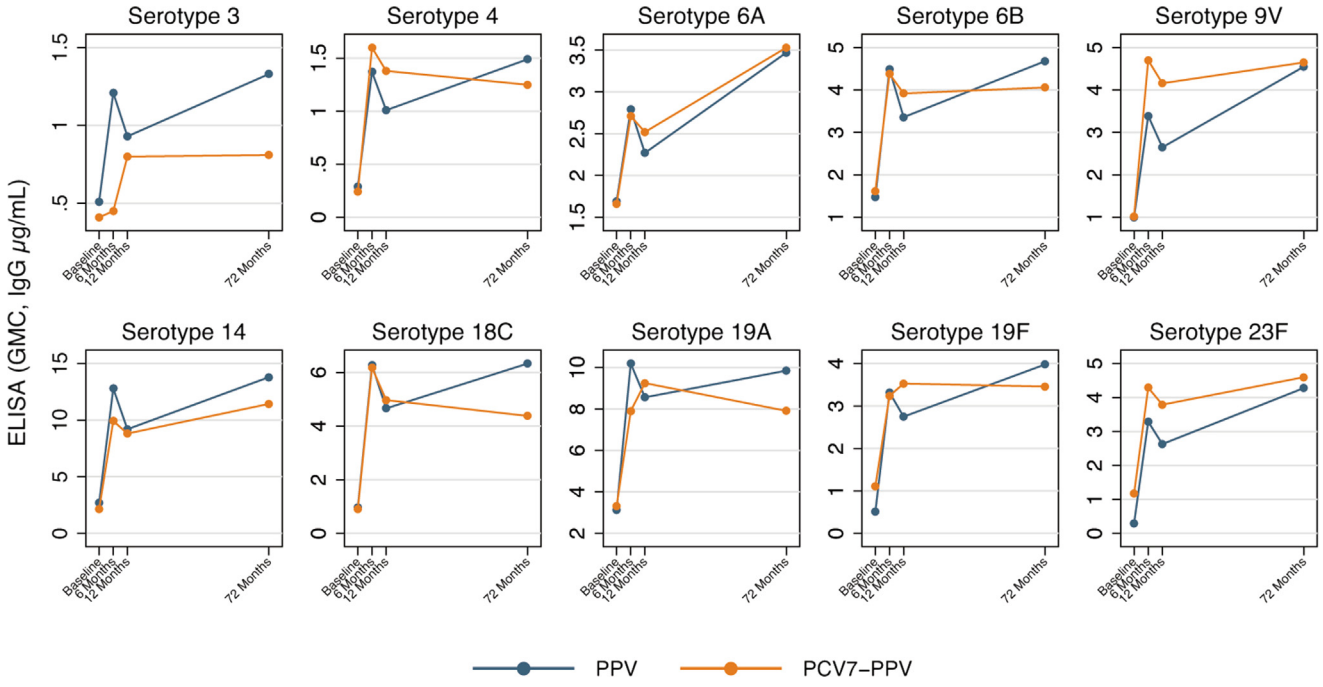

Fig. 2. ELISA (GMC, IgG μg/mL) by study arm at each time point for each of 10 serotypes.

3.2. Opsonophagocytic antibody (OPA) levels

Table 3 shows geometric mean titres (GMT) of OPA responses for both vaccines at 72 months. OPA levels from other time points in the initial trial have been published elsewhere [16]. There were no significant differences in OPA GMT between the two study arms.

Fig. 3 illustrates the changes in GMT for both study arms between baseline and the 72 months follow up visit. At the 72 months follow up visit, OPA levels in both study arms dropped to or below baseline levels for serotypes 4, 6A, 6B, 9V, and 23F. GMTs were greater than baseline levels for serotypes 14, 18C, and 19A at the 72 months follow up visit. For serotype 19F, OPA GMT remained greater than baseline for the PPV arm, but dropped to baseline levels in the PCV7-PPV arm. OPA GMT decreased between the 12 months and 6 years follow up visits for all serotypes in both study arms.

There was a significant correlation between ELISA and OPA titre for each given serotype (results not shown).

3.3. Impact of frailty on immune response

As shown in Fig. 4, GMC as measured by ELISA at 72 months follow up was significantly higher among subjects in the PCV7-PPV arm with a low frailty index compared to subjects in the PCV7-PPV arm with a moderate or high frailty index for serotypes 4 and 18C ($p = 0.01$ and $p < 0.01$, respectively). ELISA GMC did not vary significantly by frailty for other serotypes, and there were no significant differences by frailty for any serotype in the PPV arm.

OPA GMT were significantly higher in subjects in the PCV7-PPV arm with a low frailty index compared to those in the PCV7-PPV arm with a moderate or high frailty index for serotypes 18C and 23F ($p = 0.03$ and $p = 0.04$, respectively), as shown in Fig. 5. GMT did not differ significantly between frailty groups for other serotypes, and there were no significant differences by frailty for any serotype in the PPV arm.

Table 3
Comparison (*t*-test) between 23v PPV and PCV7-23vPPV for OPA in GMT (titre^{-1}).

Serotype	*GMT (95% CI) at 6 years follow up*		
	23vPPV (n = 62)	PCV7-23vPPV (n = 75)	p-value
4	63 (34, 120)	57 (32, 101)	0.99
6A	46 (25, 85)	65 (38, 112)	0.99
6B	101 (56, 182)	85 (47, 152)	0.99
9V	70 (38, 126)	125 (68, 231)	0.95
14	356 (205, 617)	314 (185, 532)	0.99
18C	255 (157, 413)	189 (109, 325)	0.99
19A	110 (73, 167)	73 (48, 113)	0.95
19F	118 (69, 203)	52 (32, 85)	0.37
23F	36 (21, 62)	49 (29, 84)	0.99

3.4. Impact of pre-vaccination immunity status on immune responses to PPV and PCV7

We compared immune responses at 72 months between trial arms among subjects who had detectable OPA at baseline (DOB) and those that had undetectable OPA at baseline (UOB). ELISA responses are displayed in Fig. 6 and OPA responses are displayed in Fig. 7. The magnitude of response at 72 months in both the PPV and PCV7-PPV groups was greater among subjects with UOB, except for serotype 6B in the PPV group. However, absolute antibody levels were higher in subjects with DOB compared to UOB for all serotypes and both study groups at 72 months, except for ELISA responses to serotypes 18C and 23F in the PCV7-PPV group.

4. Discussion

We have shown that serological immunity, especially as evidenced by IgG levels, to pneumococcal antigens in hospitalised older adults persists above baseline levels six years after vaccination for serotypes 3, 4, 6A, 6B, 9V, 14, 18C, 19A, 19F, and 23F. Waning was demonstrated between 12 months and six years for OPA, but not for ELISA levels, which remained constant or increased. Whilst PCV7 followed by PPV23 vaccination resulted in modest boosting at 12 months for some serotypes common to both vaccines, the differences between arms did not persist over the

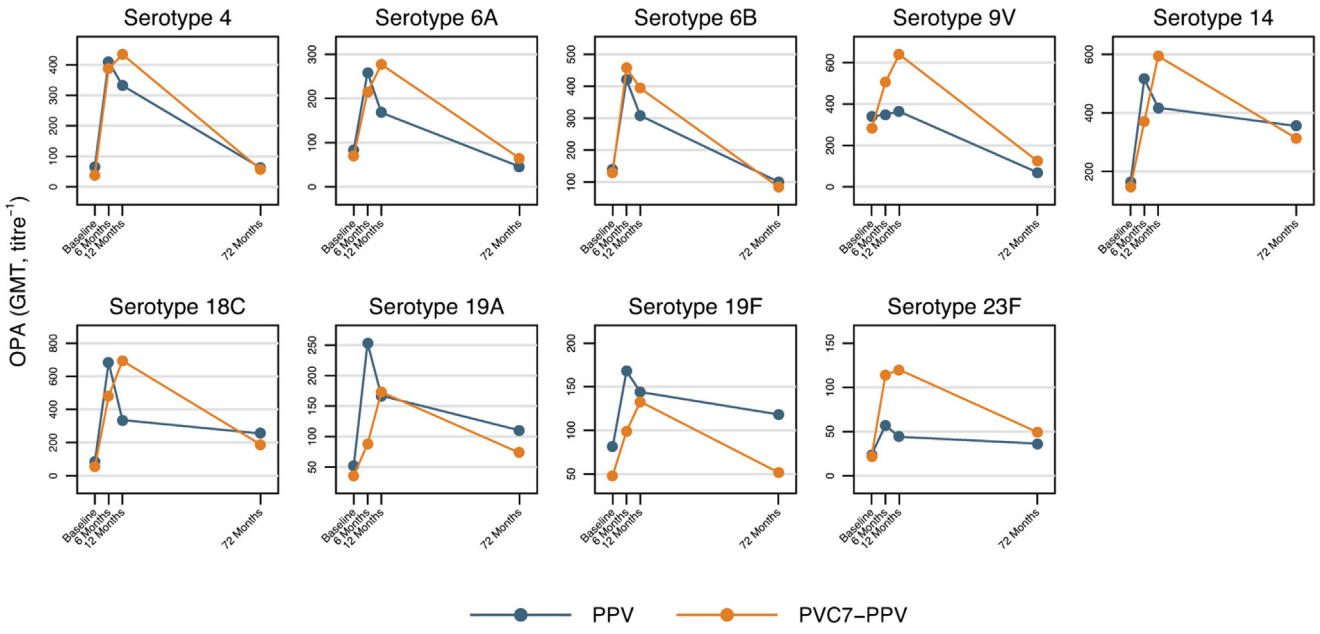

Fig. 3. OPA (GMT, titre^{-1}) by study arm at each time point for each of 9 serotypes.

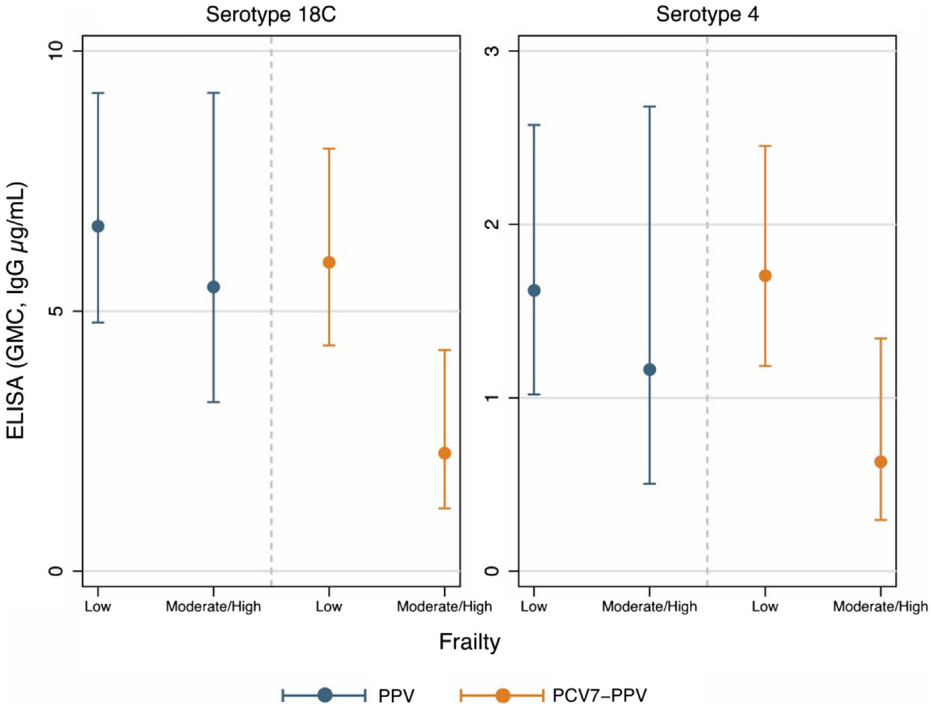

Fig. 4. Comparison of immune response[a] (GMC of ELISA, IgG μg/mL) at 72 months between low frailty[b] (≤10) and moderate/high frailty (>10) groups. [a]Significant difference between low and moderate/high frailty for *t*-test, $p \leq 0.05$. [b]Frailty assessed using modified Frailty Index.

subsequent five years. There were no significant differences in immune responses between the two study arms for any of the serotypes tested at 72 months. Whilst there are no clearly defined correlates of protection, OPA is believed to be a better measure of functional protection [27]. Although antibody levels stayed above baseline for many serotypes, it's not known whether this correlates to clinical protection.

Compared to other long-term pneumococcal vaccine studies, this is the longest follow up study directly comparing the immunogenicity of polysaccharide and conjugate vaccines in adults [28]. The only long-term study comparing the immunogenicity of the two vaccines we identified was in COPD patients followed for two years, who received either PCV7 or 23vPPV, with no 23vPPV dose post PCV7. After two years, OPA responses were significantly higher for PCV7 group for 4 of 7 serotypes tested, including serotypes 4, 14, 18C, and 23F [28].

A previous long-term study of immunogenicity of 23vPPV alone, which followed a similar study population (similar age, high prevalence of comorbidities), found that 10 years after a first PPV23 dose, ELISA IgG GMCs for all serotypes tested, except

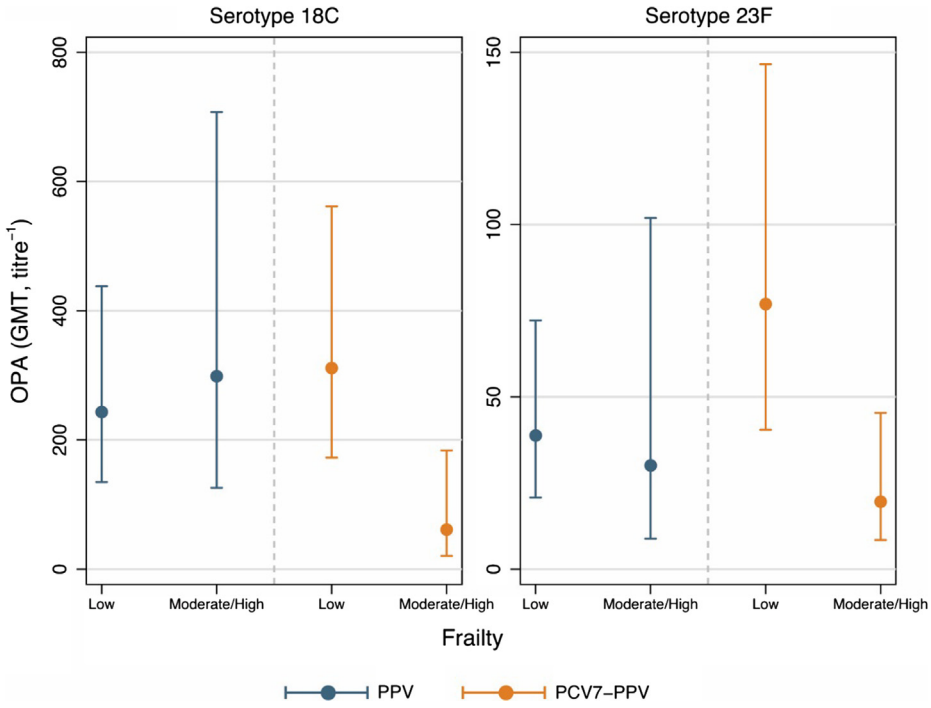

Fig. 5. Comparison of immune response[a] (GMT of OPA, titre^{-1}) at 72 months between low frailty[b] ($\leq$10) and moderate/high frailty (>10) groups. [a]Significant difference between low and moderate/high frailty for *t*-test, $p \leq 0.05$. [b]Frailty assessed using modified Frailty Index.

serotype 3, remained greater than baseline, but significantly so only for serotype 6B [18]. A small study among nursing home residents in Santiago, Chile found that antibody titres, as measured by ELISA, in individuals that received 23vPPV remained higher than baseline at two years for all serotypes tested (1, 3, 4, 5, 6B, 9V, 14, 18C, 19F, 23F) [29]. Another study measured IgG GMC's by ELISA in a large cohort of healthy older adults (aged 50 and over) five years after vaccination or revaccination with 23vPPV. For serotypes 4, 6B, 8, 9V, 12F, 14, and 23F, GMC's remained higher than baseline levels for 5 years following primary vaccination, while they fell to baseline levels after 1 year for serotype 3 [19]. Whilst consistent with our ELISA findings, these studies did not measure functional antibody.

Another immunogenicity study of PPV23 conducted among older adults, recruited from health centres and two nursing homes, found that ELISA antibody GMCs decreased significantly between one and three years follow up, but were still significantly higher than baseline levels for serotypes 4, 9V, 14, and 23F, but not for serotypes 6B and 19F [30].

Studies of conjugate vaccines alone in older people have investigated the 13 valent vaccine, which includes 1, 3, 5, 6A, 7F and 19A in addition to 7vPCV. A study among adults between the ages of 55 and 65 found that following a single dose of PCV13, IgG and OPA antibody levels to all vaccine serotypes (except IgG GMC to serotype 3) dropped but remained above baseline 5 years after vaccination [22]. The larger CAPiTA study also showed that a single dose of PCV13 produced OPA titers and IgG concentrations for all 13 vaccine serotypes that remained significantly greater than baseline, and the corresponding responses in the placebo group, for 24 months post-vaccination [21]. These studies were consistent with our OPA findings.

In 2017, there were a total of 2044 notifications of invasive pneumococcal disease in Australia, which was a 22% increase relative to 2016. Serotype 3 was the most common serotype identified, causing approximately 12.7% of total cases and 14.0% of cases in people over 65 years of age. Serotype 19A was responsible for 6.2% of total reported IPD cases, and for 6.0% of cases in people over 65.

The introduction of universal infant PCV7 vaccination in Australia in 2005 decreased overall IPD incidence due to herd immunity but increased the incidence of IPD caused by non-vaccine serotypes, particularly serotype 19A [31]. As a result, PCV7 for infants was replaced by PCV13 in the National Immunisation Program in 2011. While this significantly decreased incidence of IPD caused by serotypes 1, 6A, and 19A, serotype 3 incidence did not decrease and the incidence of non-13vPCV serotypes has increased. Similar trends in serotype replacement have been observed in other high-income countries following the introduction of infant pneumococcal conjugate vaccines [32]. In the UK, the decline in IPD incidence from PCV serotypes among older adults has been largely offset by an increase in IPD incidence from non-PCV serotypes, even with high coverage of 23vPPV in people over 65 [33]. This highlights the need to re-examine pneumococcal vaccination strategies for older adults, as the herd immunity benefits from infant PCV vaccination may not result in long-term decreases in IPD incidence in older adults.

A change in recommendations occurred in 2011 in Australia from 5 yearly booster to a single dose of 23vPPV for people aged > 65 years without risk factors for IPD [34]. Our study showed substantial waning of OPA for several serotypes at 6 years for both arms, which is a concern given the single dose recommendation. Approximately 5.2% of total IPD cases and 6.0% of cases in people over 65 were attributed to serotype 19F [35–38]. Although prevalence of 23F pneumococcal carriage is low in Australia and has decreased in Aboriginal people in Western Australia, serotype 23F isolates in Australia have demonstrated high rates of multidrug resistance [39]. Therefore, the weak immune response to 23F observed in both vaccine groups is particularly concerning and warrants further research. The waning of OPA titres to baseline levels for serotypes 4, 6A, 6B, 9V, 19F, and 23F are also concerning in light of the single dose recommendation. The impact of PCV13 recommendations on IPD and pneumococcal pneumonia in the

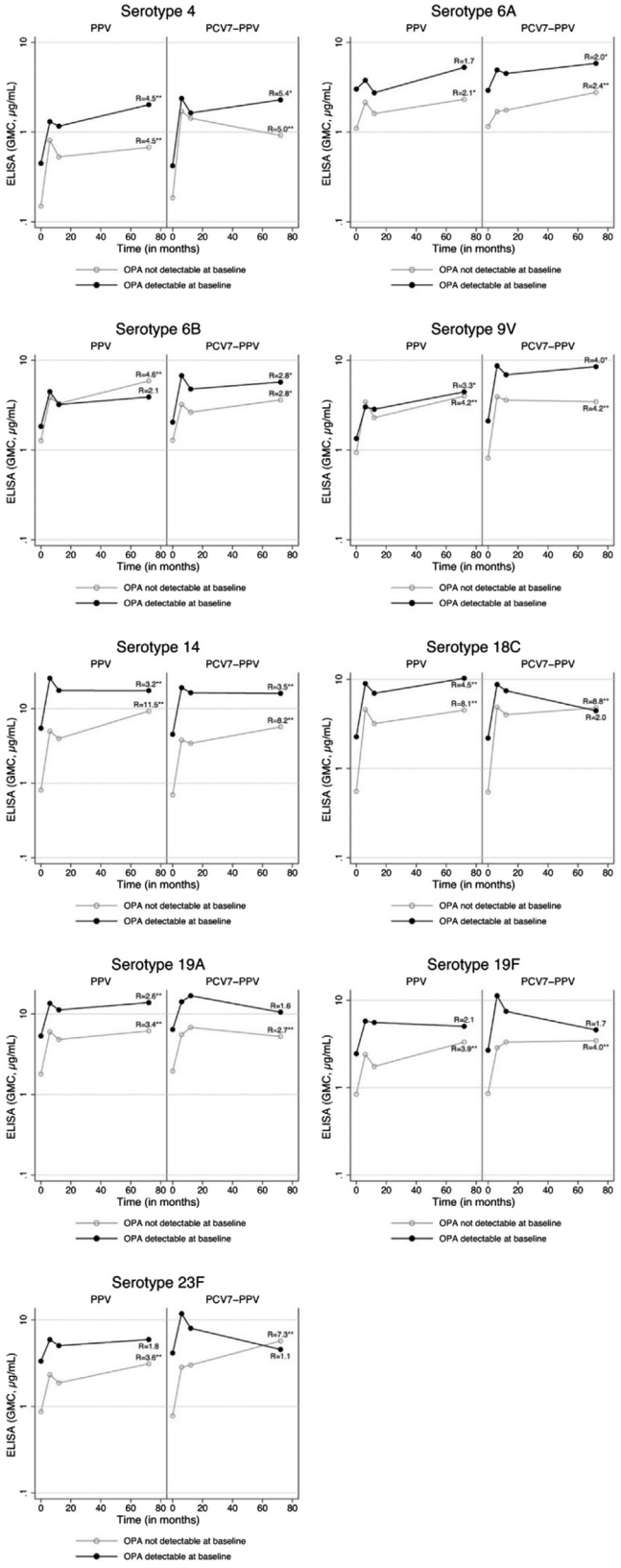

Fig. 6. ELISA (GMC, IgG μg/mL) by time point based on baseline OPA titre (i.e. detectable or not detectable) for each of 9 serotypes: 4, 6A, 6B, 9V, 14, 18C, 19A, 19F, 23F (R = ratio to baseline; * significant difference from baseline for paired *t*-test, $p \leq 0.05$; **highly significant difference from baseline for paired *t*-test, $p \leq 0.01$.

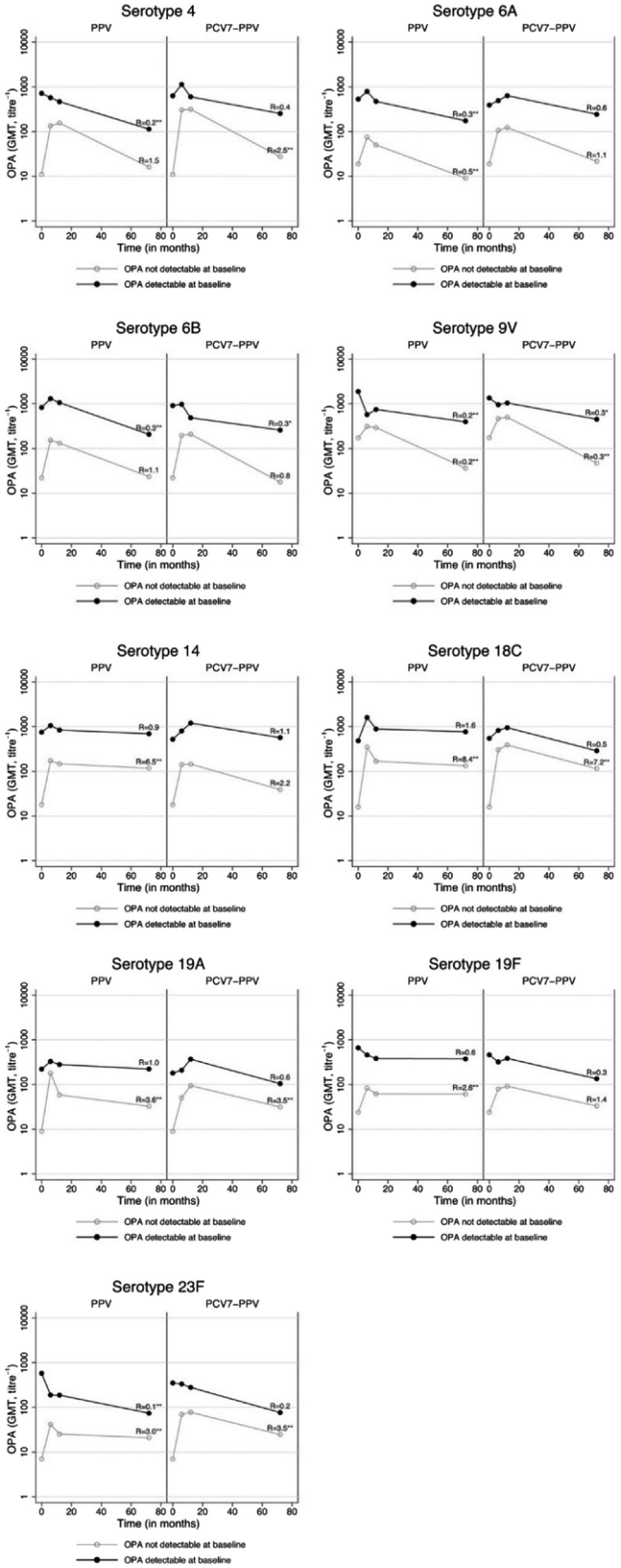

Fig. 7. OPA (GMT, titre^{-1}) by time point based on baseline OPA titre (i.e. detectable or not detectable) for each of 9 serotypes: 4, 6A, 6B, 9V, 14, 18C, 19A, 19F, 23F (R = ratio to baseline; * significant difference from baseline for paired *t*-test, $p \leq 0.05$; **highly significant difference from baseline for paired *t*-test, $p \leq 0.01$).

US is currently being reviewed by the ACIP [40] and the role of PCV13 in relation to the current 23vPPV program is being assessed in Australia [41]. A proposal to remove routine vaccination for adults aged 65–74 years is currently being considered as of June 2019 [42].

Similar to our initial trial, increasing frailty and weaker baseline immunity (as determined by undetectable OPA at baseline) predicted poorer overall immune responses to some serotypes at 72 months. However, individuals with low baseline immunity had a greater magnitude of response at 72 months to both vaccination schedules compared to those with detectable OPA at baseline. We observed similar results in our initial study. This highlights the importance of vaccinating frail older adults despite weaker immunity, because they may still be able to mount a protective response even if their final antibody levels are lower than less frail adults. This is an important finding, given that older adults (aged 80 and over) with complex comorbidities are generally less likely to receive pneumococcal vaccine from their medical providers in Australia [43].

This study was not without limitations. Because this was a 6 year follow up of hospitalised, frail older adults, there was significant loss to follow up in both study arms, primarily due to death of participants (unrelated to vaccination). Only half of participants recruited for the initial trial completed the 6 year follow up. As such, it is unclear if there was sufficient statistical power to determine any differences in immue response between the two study arms. In addition, patients with lower frailty were more likely to survive the entire follow up period, and thus immune responses after 6 years may be biased towards higher values. Since participants were initially recruited during hospitalisation, reflecting a more frail and ill population, the findings in this study may not be generalisable to healthy, older adults. Whilst subjects with higher ELISA titres also had higher OPA titres, ELISA results remained high, whilst OPA waned during long term follow up. It is generally accepted that the OPA results are thought to better reflect functional protection. These data provide reassurance that antibody levels for some serotypes remain above baseline beyond 5 years in frail elderly recipients of pneumococcal vaccines, including those with no measurable antibody pre-vaccination. Whether this translates to continued protection is unknown, but possible. More research is required to inform dosing and scheduling of vaccination for long term protection, especially in light of the single dose PPV reccomendation in Australia. Vaccinology in older adults hold promise, as has recently been seen with a novel adjuvant and high efficacy against herpes zoster in older people [44–46]. Further reductions in IPD and pneumonia in the high risk frail elderly population may require new vaccine technology.

Declaration of Competing Interest

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