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Original article

Immunogenicity and safety of the 13-valent Pneumococcal Conjugate vaccine in 23-valent pneumococcal polysaccharide vaccine-naive and pre-immunized patients under treatment with chronic haemodialysis: a longitudinal quasi-experimental phase IV study

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ABSTRACT

Objective: To benchmark the immunogenicity of pneumococcal conjugated vaccine (PCV-13) versus pneumococcal polysaccharide vaccine (PPV-23) in haemodialysis patients pre-vaccinated or not with PPV-23.
Methods: The study is a longitudinal quasi-experimental phase IV study in chronic haemodialysis patients aged ≥50 years. Total (ELISA) and functional (opsonophagocytic assay) antibodies after pneumococcal vaccination were quantified at baseline, and after 28 and 365 days. Of 201 eligible patients, 155 were included. Patients were divided in four groups. PPV-23 naive patients were randomized to PPV-23 (40) or PCV-13 (40) vaccination. PPV-23-pre-vaccinated patients were categorized as being vaccinated more (40) or less (35) than 4 years before the study and all received PCV-13.
Results: Patients among the four groups had a significant ELISA antibody response for most serotypes that remained significant up to day 365 versus baseline. In PPV-23-naive patients, ELISA antibody titres were significantly higher among PCV-13 versus PPV-23 recipients for six serotypes (1.85–2.34-fold) after 28 days, and remained significantly higher for one serotype (6A, 1.57-fold) after 365 days. Following PCV-13 vaccination, increase in ELISA antibody titres was significantly higher among PPV-23-naive versus PPV-23-pre-vaccinated patients for 12 serotypes after 28 days (1.68–7.74-fold) and remained significantly higher in ten serotypes (1.44–3.29-fold) after 365 days.
Conclusion: Immune response after PPV-23 and PCV-13 remains significant for at least 1 year in non-PPV-23-pre-vaccinated patients. Among vaccine-naive haemodialysis patients PCV-13 seems more immunogenic than PPV-23. Immune response to PCV-13 is weaker in PPV-23-pre-vaccinated compared with vaccine-naive patients. **S.J. Vandecasteele, Clin Microbiol Infect 2018;24:65**

Introduction

Pneumococcal polysaccharide vaccines induce a T-cell-independent B-cell response [1], but are poorly immunogenic in young children, the elderly and immunocompromised patients [2]. Pneumococcal polysaccharide vaccines (PPV) decrease the incidence of invasive pneumococcal disease, but their impact on non-invasive pneumococcal disease is less clear [1]. Pneumococcal conjugated vaccines (PCV) were developed to improve pneumococcal vaccine immunogenicity. PCV induce both a T-cell and B-cell response and an immunological memory. PCV-13 covers 61% of invasive pneumococcal disease strains in Belgium [3]. Universal PCV-7 childhood vaccination was introduced in 2004 in Belgium, and replaced by the PCV-13 in 2011. In a large, prospective, population-based placebo-controlled study in people >65 years of age (CaPiTa trial), PCV-13 vaccination was associated with a 45% decrease in vaccine-type pneumonia and a 75% decrease in vaccine-type invasive pneumococcal disease, without decreasing overall pneumonia incidence and mortality [4].

Pneumonia incidence in patients with end-stage renal disease (ESRD) is 27.9/100 person-years, with a 1 year survival rate of only

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0.51 [5–8]. Data on the efficacy of pneumococcal vaccination in patients with ESRD are scarce and hampered by multiple methodological issues. Guidelines recommending pneumococcal vaccination in patients with ESRD are mainly based on extrapolations from the general population in conjunction with population-specific epidemiological and serological data [1]. Two large retrospective cohort studies in patients undergoing haemodialysis demonstrated a hazard rate for mortality of 0.84 [9] to 0.94 [10] for pneumococcal vaccination alone, and of 0.71 [9] to 0.73 [10] for combined pneumococcal and flu vaccination. This beneficial correlation does not, however, prove causality. Eleven studies with polysaccharide vaccines (only three with PPV-23) were performed in patients with ESRD [11]. Most of these trials were small (only two with >33 patients), non-randomized and had a limited follow up of only 6–12 months [1,11–13]. Overall, a serological response to at least some of the serotypes was documented in the majority of patients, which tended to be lower and more rapidly waning than in healthy controls [1,11]. One-fifth of vaccinated patients developed pneumococcal disease in the long term [1]. Two small trials studied conjugated pneumococcal vaccines. In the first, more than half of 48 children vaccinated with PCV-7 were non-responders, defined as the absence of a more than four-fold rise in antibody levels for at least five serotypes [14]. In the second, PCV-13 vaccination in 25 adult dialysis patients resulted in a certain antibody response at 2 months that grossly disappeared after 1 year [15].

The current study aimed to benchmark the immunogenicity of PCV-13 vaccine compared with the PPV-23 vaccine in patients with ESRD treated with chronic haemodialysis that were pre-vaccinated, or not, with PPV-23.

Materials and methods

Trial design

The study is a longitudinal quasi-experimental phase IV study in chronic haemodialysis patients aged ≥50 years benchmarking immune response to pneumococcal vaccination (Fig. 1). All eligible patients were classified according to their PPV-23 vaccination status. Eligible PPV-23-naive patients were randomized according to the alphabetical order of the first letter of their name to vaccination with either PPV-23 (group 1) or PCV-13 (group 2). PPV-23-pre-vaccinated patients were classified as vaccinated more (group 3) or less (group 4) than 4 years before the study, and were all vaccinated with PCV-13. In group 3, patients were selected listed according to the alphabetical order of their name, and only the 40 first patients were included. Initially a 5-year cut-off was foreseen to differentiate recent from older PPV-23 vaccination, but this yielded almost no group 3 patients due to the high 5-year mortality of dialysis patients.

Participants

Patients were eligible if (a) treated with chronic haemodialysis, (b) ≥50 years of age, (c) not pregnant, (d) without immediate life-threatening conditions, (e) without allergy to the vaccines, (f) with pneumococcal vaccination status documented in the medical files, and (g) gave their informed consent. All patients were treated in two dialysis centres in Belgium (AZ Sint-Jan Brugge-Oostende AV in Bruges, Onze Lieve Vrouw Ziekenhuis in Aalst).

Interventions

The PPV-23 vaccine, Pneumo 23™ (Sanofi Pasteur MSD, Brussels, Belgium) contained antigens to 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F. The PCV-13 vaccine, Prevenar 13™ (Weyth Lederle Phizer, Louvain-la-Neuve, Belgium) contained antigens to 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. All vaccines were administered intramuscularly on the 24 and 25 of February 2013. Baseline blood samples were taken on the day of vaccination, at the start of dialysis treatment. Vaccination was given at the end of the same dialysis treatment, about 3.5 h later.

Outcomes

The primary endpoint was the ELISA and opsonophagocytic assay (OPA) antibody response after 4 and 52 weeks compared with

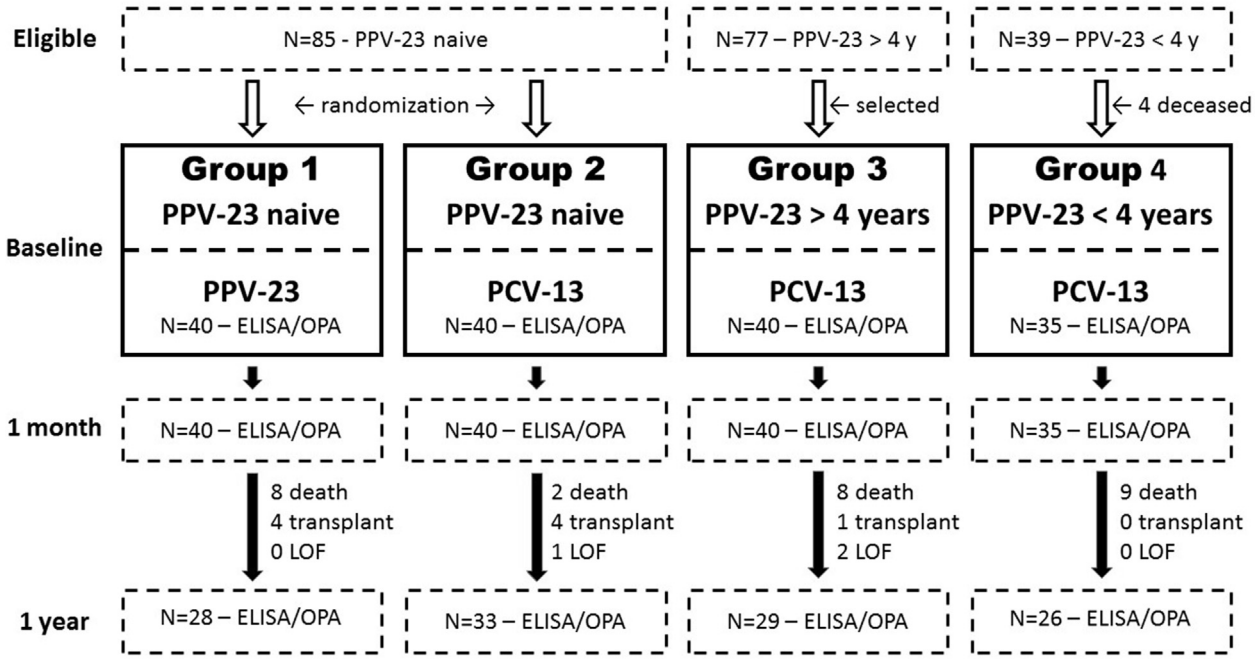

Fig. 1. Study design and outcome (LOF, lost to follow up; transplant, kidney transplantation).

baseline titres. ELISA and OPA antibody titres to the common PPV-23 and PCV-13 antigens (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) and to the PCV13 (6A) specific serotype 6A were quantified as previously described [16,17].

The secondary endpoints were:

(a) Vaccine adverse effects. Patients registered daily sublingual temperature, analgesic use, fatigue, generalized muscle aches, headache, and itching, pain, or subjectively reported decreased mobility in the vaccinated arm for 7 days. Severity levels were I (present, but easily tolerated), II (interfering with daily activity) or III (severe or debilitating). Before vaccination, and on subsequent dialysis sessions (48, 72 and 96 h), trained nurses registered the area of redness, discoloration and localized swelling in the vaccinated arm by placing a transparent sheet with circles of various diameters (ranging from 1 to 15 cm) on the vaccinated arm. Severity levels were I (<8 cm), II (≥8 and <15 cm), and III (≥15 cm).
(b) Patient mortality and pneumonia (defined as acute respiratory illness with a new infiltrate on chest X-ray) incidence.

Additional sub-analyses of the primary outcome data compared differences in antibody response in PPV-23-naive patients after PCV-13 versus PPV-23 vaccination, differences in antibody response after PCV-13 vaccination in PPV-23-naive versus PPV-23-pre-vaccinated patients, and differences in antibody response after PCV-13 vaccination in patients that were previously vaccinated with the PPV-23 vaccine >4 years versus <4 years earlier.

Sample size

The study was designed as a benchmark trial. Given the lack of any information on the effect of PCV-13 vaccination in dialysis patients, and the absence of a clear single number primary outcome parameter (geometric mean titre (GMT) for specific serotype), no primary power analysis was done.

Statistical methods

Baseline characteristics of patients were summarized according to the mean and standard deviation (SD), median and interquartile range (P25–P75) or percentages. Their distribution was statistically compared between the four groups using Fisher's exact test for categorical data and the Kruskal–Wallis test for continuous data. Patient outcomes and incidences of adverse effects were compared according to the Fisher's exact test. Antibody responses were summarized as the GMT by back-transforming (calculating the antilog) of average log-transformed titres. Equally, two-sided 95% CIs were constructed by back-transformation of the CIs for the mean of the logarithmically transformed assay results, computed using the Student's *t* distribution. Differences in GMTs between two groups (or changes in GMTs from baseline to 28 days and from baseline to 365 days), were expressed as GMT ratios calculated by back transforming the mean differences between vaccine groups (or time-points) on the logarithmic scale. GMT ratios were considered statistically significant if their 95% CI did not include the value 1. Differences in GMT ratios were evaluated according to the Mann–Whitney *U* test for two independent samples. All analyses were carried out using SAS software (release 9.4; Cary, NC, USA).

Informed consent and institutional review

All patients provided written informed consent before inclusion. The protocol was approved by the Ethical Committee of both hospitals. ClinicalTrials.gov registration number is NCT02492438.

Results

Patients

Baseline patient characteristics are summarized in Table 1. From the 85 eligible PPV-23-naive patients, 40 were randomized to vaccination with PPV-23 (group 1), and 40 to vaccination with PCV-13 (group 2). From the 77 eligible patients that were pre-vaccinated with PPV-23 >4 years earlier, 40 were selected for PCV-13 vaccination (group 3). Among the 39 eligible patients that were pre-vaccinated with PPV-23 <4 years earlier, four died between inclusion in the study and start of the study, leaving 35 patients that were vaccinated with PCV-13 (group 4). Patients in the PPV-23-pre-vaccinated groups 3 and 4 had a higher dialysis vintage, and,

Table 1
Baseline patient characteristics

	Group 1 PPV-23-naive PPV-23 vaccine	Group 2 PPV-23-naive PCV-13 vaccine	Group 3 PPV-23 >4 years PCV-13 vaccine	Group 4 PPV-23 <4 years PCV-13 vaccine	p value[c]
n	40	40	40	35	
Men, *n* (%)	23 (57.5%)	25 (62.5%)	17 (42.5%)	23 (65.7%)	0.172
Age (years)[a]	72.4 (13.4)	68.3 (13.9)	74.8 (8.7)	74.6 (8.2)	0.204
Vintage (years)[b]	2.04 (0.82–4.85)	2.45 (1.41–3.87)	3.40 (2.48–5.09)	2.83 (1.46–6.30)	0.030
Underlying disease, *n*					
Vascular	24	19	20	16	0.606
Diabetes	9	9	9	11	0.750
Glomerulonephritis	3	3	4	2	0.976
Cystic	0	3	2	0	0.171
Interstitial	2	5	4	1	0.393
Other	2	1	1	5	0.172
Laboratory values					
Haemoglobin (g/dL)[a]	10.8 (1.2)	11.0 (1.2)	10.9 (1.0)	10.8 (1.4)	0.795
Urea (mg/dL)[a]	118.2 (40.8)	127.4 (44.7)	147.1 (36.6)	144.7 (45.5)	0.008
Albumin (g/dL)[a]	37.3 (4.1)	38.3 (3.5)	37.8 (3.1)	37.0 (4.2)	0.543
Phosphate (meq/L)[a]	1.63 (0.67)	1.51 (0.44)	1.49 (0.30)	1.62 (0.40)	0.834
C-reactive protein (mg/L)[b]	7.24 (3.55–16.65)	6.30 (2.92–17.21)	7.28 (2.65–17.24)	6.30 (1.68–22.08)	0.778

Abbreviations: PCV-13, pneumococcal conjugated vaccine; PPV-23, pneumococcal polysaccharide vaccine.
Data are given as.
[a] mean (SD) or.
[b] median (P25–P75).
[c] Significance is given according to Fisher's exact test for categorical data or the Kruskal–Wallis test for continuous data.

consequently, a higher pre-dialysis blood urea, reflecting a lower residual kidney function.

Antibody response after pneumococcal vaccination

Primary endpoint: overall antibody response after 28 and 365 days compared with baseline (Tables 2 and 3)

For group 1 patients (PPV-23-naive, PPV-23 vaccine), GMT antibody titres were significantly higher for all serotypes at day 28 (ELISA: 1.3- to 6.5-fold; OPA: 3.9- to 40.7-fold), and remained significantly higher for 12 serotypes at day 365 (ELISA: 1.6- to 4.2-fold; OPA: 1.8- to 11.5-fold). For group 2 patients (PPV-23-naive, PCV-13 vaccine), GMT antibody titres were significantly higher for all serotypes at day 28 (ELISA: 2.2- to 10.6-fold; OPA: 2.8- to 63.7-fold), and remained significantly higher for 12 serotypes at day 365 (ELISA: 2.1- to 6.0-fold; OPA: 2.5- to 21.5-fold). For group 3 patients (PPV-23 >4 years, PCV-13 vaccine), GMT antibody titres were significantly higher for 12 serotypes at day 28 (ELISA: 1.1- to 2.5-fold; OPA: 1.5- to 7.5-fold), and remained significantly higher in three serotypes with OPA and nine serotypes with ELISA at day 365 (ELISA: 1.3- to 2.0-fold; OPA: 1.6- to 2.3-fold). For group 4 patients (PPV-23 <4 years, PCV-13 vaccine), GMT antibody titres were significantly higher for 12 serotypes at day 28 (ELISA: 1.4- to 2.7-fold; OPA: 1.7- to 10.8-fold), and remained significantly higher for nine serotypes with OPA and 12 with ELISA at day 365 (ELISA: 1.6- to 2.6-fold; OPA: 1.4- to 6.7-fold).

Differences in antibody response in PPV-23-naive patients after PCV-13 versus PPV-23 vaccination (Table 4)

At baseline, antibody titres did not differ among the two groups. At day 28, GMT of ELISA titres provoked by PCV-13 versus the PPV-23 were 1.85- to 2.34-fold higher for six serotypes. The GMT of OPA titres did not differ. At day 365, these differences had waned (only significant for GMT of ELISA for serotype 6A, 1.57-fold).

Differences in antibody response after PCV-13 in PPV-23-naive (group 2) versus PPV-23-pre-vaccinated patients (groups 3 and 4) (Table 5)

At baseline, GMT antibody titres were significantly lower in non-PPV-23-pre-vaccinated patients for two (ELISA) to four (OPA) serotypes versus PPV-23-pre-vaccinated patients (groups 3 and 4). Antibody response after PCV-13 vaccination was, however, much higher and longer lasting in the non-PPV-23-pre-vaccinated group 2 patients than in the PPV-23-pre-vaccinated groups 3 and 4 patients (ELISA: 1.68- to 4.75-fold for 12 serotypes at day 28 and 1.44- to 3.29-fold for ten serotypes at day 365; OPA: 1.73- to 9.63-fold for 11 serotypes at day 28 and 2.43- to 7.78-fold for nine serotypes at day 365).

Differences in antibody response after PCV-13 in patients that were vaccinated with the PPV-23 <4 years ago (group 4) versus >4 years ago (group 3)

At baseline and day 28, no differences were observed. At day 365, patients pre-vaccinated <4 years ago had higher GMT antibody titre for four serotypes, but results were incongruent for ELISA (1.52- to 1.72-fold, serotypes 7F, 14 and 19F) and OPA (1.45- to 3.47-fold, serotypes 1, 3, 4 and 6A).

Clinical outcome

Outcome data are summarized in the Supplementary material (Table S1). One-year mortality was 17.4%, and did not differ significantly among the treatment groups, although there was a trend for lower all-cause mortality in the non-PPV-23-pre-vaccinated group that received a PCV-13 vaccine (p 0.055). One-year

Table 2
Antibody response at 4 weeks compared with baseline titres

	Group 1 PPV-23-naive + PPV-23 vaccine				Group 2 PPV-23-naive + PCV-13 vaccine				Group 3 PPV-23 >4 years + PCV-13 vaccine				Group 4 PPV-23 <4 years + PCV-13 vaccine			
	N	GMT_0	GMT_4	GMT ratio (95% CI)[a]	N	GMT_0	GMT_4	GMT ratio (95% CI)	N	GMT_0	GMT_4	GMT ratio (95% CI)	N	GMT_0	GMT_4	GMT ratio (95% CI)
ELISA																
1	35	0.22	1.40	6.5 (4.1–10.3)	35	0.19	1.80	9.4 (5.3–16.8)	39	0.49	0.83	1.7 (1.3–2.2)	30	0.57	1.37	2.4 (1.6–3.6)
3	27	0.12	0.22	1.9 (1.3–2.6)	30	0.13	0.29	2.2 (1.6–3.1)	27	0.15	0.17	1.1 (1.0–1.3)	26	0.15	0.23	1.5 (1.1–2.0)
4	37	0.09	0.44	4.8 (3.1–7.4)	38	0.09	0.99	10.6 (6.2–18.3)	40	0.19	0.47	2.4 (1.8–3.3)	31	0.19	0.61	3.2 (2.0–5.1)
5	37	1.29	1.63	1.3 (1.1–1.5)	35	1.26	3.71	3.0 (2.0–4.4)	34	1.82	2.64	1.4 (1.2–1.7)	30	1.08	1.54	1.4 (1.1–1.9)
6A	30	0.83	1.23	1.5 (1.1–2.0)	36	0.90	2.66	3.0 (2.0–4.3)	35	0.60	1.29	2.1 (1.4–3.4)	29	0.83	2.28	2.7 (1.7–4.5)
6B	30	0.45	1.60	3.5 (2.4–5.2)	34	0.76	3.37	4.4 (2.7–7.3)	35	0.69	1.73	2.5 (1.7–3.7)	28	0.83	1.67	2.0 (1.4–2.9)
7F	38	0.60	2.15	3.6 (2.6–5.0)	39	0.74	6.08	8.2 (4.5–15.0)	40	1.21	1.92	1.6 (1.3–2.0)	32	0.81	1.82	2.2 (1.6–3.2)
9V	38	0.55	1.48	2.7 (2.1–3.6)	37	0.65	3.24	5.0 (3.2–7.9)	40	0.89	1.69	1.9 (1.4–2.5)	32	0.79	1.54	1.9 (1.5–2.5)
14	37	1.55	6.40	4.1 (2.4–7.0)	39	1.87	10.30	5.5 (3.2–9.5)	37	1.91	3.36	1.8 (1.4–2.3)	32	2.03	4.26	2.1 (1.4–3.1)
18C	37	0.58	2.26	3.9 (2.7–5.6)	39	0.61	3.79	6.2 (3.9–9.8)	38	1.18	2.53	2.1 (1.6–2.8)	30	0.94	2.45	2.6 (1.7–3.9)
19A	38	1.63	3.00	1.8 (1.5–2.3)	38	1.55	5.60	3.6 (2.3–5.6)	40	2.02	4.03	2.0 (1.5–2.7)	30	1.50	2.87	1.9 (1.4–2.6)
19F	38	0.47	1.11	2.4 (1.7–3.3)	35	0.62	2.02	3.2 (2.0–5.3)	39	0.66	1.04	1.6 (1.3–1.8)	28	0.99	1.83	1.9 (1.2–2.8)
23F	37	0.56	1.35	2.4 (1.7–3.4)	36	0.96	3.22	3.3 (2.0–5.4)	37	0.75	1.25	1.7 (1.3–2.2)	31	0.76	1.37	1.8 (1.3–2.4)
OPA																
1	35	5.64	45.21	8.0 (4.5–14.4)	35	5.63	55.73	9.9 (5.4–18.2)	30	9.66	21.78	2.3 (1.5–3.4)	26	9.88	26.14	2.6 (1.5–4.6)
3	36	4.48	26.39	5.9 (3.8–9.2)	34	6.21	17.33	2.8 (1.7–4.4)	31	8.07	12.31	1.5 (1.1–2.2)	27	8.04	13.73	1.7 (1.2–2.4)
4	22	7.83	318.76	40.7 (12.2–135.3)	27	5.59	355.89	63.7 (20.9–193.8)	20	23.65	149.16	6.3 (2.7–14.6)	20	36.94	256.13	6.9 (2.3–21.1)
5	35	4.63	18.05	3.9 (2.3–6.5)	36	5.19	72.43	14.0 (6.8–28.8)	31	11.31	36.20	3.2 (1.9–5.4)	25	12.21	47.18	3.9 (2.1–7.1)
6A	32	12.54	225.15	18.0 (7.7–41.8)	34	26.22	746.89	28.5 (11.8–69.1)	29	42.42	316.70	7.5 (2.9–18.9)	25	32.68	352.85	10.8 (3.4–34.6)
6B	21	23.92	355.95	14.9 (5.5–40.3)	28	31.56	675.85	21.4 (7.9–57.8)	20	107.73	378.39	3.5 (1.4–8.8)	21	51.28	265.74	5.2 (1.9–14.1)
7F	36	12.92	243.51	18.9 (8.9–40.0)	31	20.49	559.61	27.3 (11.1–67.3)	31	48.22	217.05	4.5 (2.4–8.4)	25	45.22	240.61	5.3 (2.5–11.3)
9V	30	34.64	309.37	8.9 (3.7–21.4)	23	40.73	401.39	9.9 (3.8–25.6)	13	66.55	258.19	3.9 (0.9–16.6)	15	52.90	302.36	5.7 (2.3–14.1)
14	22	30.10	560.51	18.6 (6.3–55.5)	23	75.15	756.37	10.1 (4.2–23.9)	5	46.41	98.04	2.1 (0.3–15.3)	14	145.82	314.30	2.2 (1.0–4.9)
18C	24	11.87	229.90	19.4 (8.5–44.0)	29	9.80	155.70	15.9 (6.6–38.1)	23	44.16	154.15	3.5 (2.0–6.0)	21	31.97	184.00	5.8 (3.2–10.4)
19A	34	19.08	124.66	6.5 (3.6–11.9)	35	16.99	144.56	8.5 (4.3–16.7)	29	63.64	205.01	3.2 (1.9–5.6)	25	37.56	102.82	2.7 (1.6–4.5)
19F	27	13.59	124.12	9.1 (4.1–20.3)	29	10.39	138.66	13.3 (5.1–34.8)	18	27.64	71.77	2.6 (1.4–4.8)	17	31.25	114.30	3.7 (1.4–9.3)
23F	22	6.54	76.53	11.7 (4.3–31.7)	28	7.72	58.51	7.6 (3.0–19.1)	20	12.06	56.17	4.7 (1.9–11.7)	19	11.47	38.21	3.3 (1.6–7.1)

Abbreviations: PCV-13, pneumococcal conjugated vaccine; PPV-23, pneumococcal polysaccharide vaccine.
[a] Geometric mean titre ratio and 95% CI.

Table 3
Antibody response at 52 weeks compared with baseline titres

	Group 1 PPV-23-naive + PPV-23 vaccine				Group 2 PPV-23-naive + PCV-13 vaccine				Group 3 PPV-23 >4 years + PCV-13 vaccine				Group 4 PPV-23 <4 years + PCV-13 vaccine			
	N	GMT_0	GMT_{52}	GMT ratio (95% CI)[a]	N	GMT_0	GMT_{52}	GMT ratio (95% CI)	N	GMT_0	GMT_{52}	GMT ratio (95% CI)	N	GMT_0	GMT_{52}	GMT ratio (95% CI)
ELISA																
1	26	0.24	0.98	4.1 (2.7–6.3)	28	0.18	0.79	4.3 (2.8–6.4)	29	0.45	0.59	1.3 (1.0–1.7)	24	0.94	1.97	2.1 (1.4–3.2)
3	18	0.11	0.14	1.3 (0.9–1.8)	19	0.12	0.14	1.2 (0.8–1.6)	21	0.14	0.14	1.0 (0.8–1.3)	18	0.15	0.21	1.4 (1.0–1.9)
4	26	0.09	0.33	3.6 (2.3–5.5)	31	0.08	0.51	6.0 (3.7–9.7)	30	0.22	0.42	1.9 (1.4–2.8)	24	0.28	0.74	2.6 (1.6–4.1)
5	27	1.23	2.36	1.9 (1.5–2.5)	30	1.20	2.62	2.2 (1.7–2.8)	27	1.80	2.09	1.2 (0.9–1.4)	23	1.50	2.33	1.6 (1.2–2.0)
6A	22	0.91	1.49	1.6 (1.3–2.1)	28	0.86	2.20	2.6 (1.8–3.6)	27	0.63	1.08	1.7 (1.1–2.6)	23	1.23	3.05	2.5 (1.5–4.0)
6B	22	0.55	1.76	3.2 (2.3–4.4)	28	0.72	2.52	3.5 (2.5–4.9)	28	0.66	1.30	2.0 (1.5–2.6)	24	1.17	2.58	2.2 (1.3–3.7)
7F	27	0.61	2.07	3.4 (2.4–4.8)	32	0.77	3.08	4.0 (2.4–6.7)	30	1.22	1.56	1.3 (1.1–1.5)	25	1.13	2.48	2.2 (1.7–2.9)
9V	27	0.49	1.15	2.3 (1.8–3.0)	30	0.73	2.25	3.1 (2.2–4.5)	30	0.98	1.39	1.4 (1.1–1.8)	25	1.12	1.94	1.7 (1.4–2.2)
14	28	1.77	7.42	4.2 (2.5–7.2)	32	1.93	9.53	4.9 (2.9–8.3)	29	2.24	2.87	1.3 (1.1–1.5)	25	2.59	4.67	1.8 (1.3–2.6)
18C	27	0.60	2.10	3.5 (2.5–5.0)	31	0.53	2.20	4.1 (2.7–6.3)	29	1.22	1.83	1.5 (1.2–1.8)	26	1.22	2.90	2.4 (1.7–3.4)
19A	27	1.61	2.83	1.8 (1.4–2.2)	31	1.57	3.62	2.3 (1.6–3.2)	30	2.36	3.45	1.5 (1.1–1.9)	26	1.89	3.39	1.8 (1.4–2.2)
19F	28	0.41	0.77	1.9 (1.4–2.5)	28	0.57	1.32	2.3 (1.5–3.5)	28	0.81	1.11	1.4 (1.2–1.6)	24	1.30	2.72	2.1 (1.4–3.1)
23F	26	0.54	1.26	2.3 (1.6–3.4)	30	1.04	2.22	2.1 (1.6–2.9)	30	0.86	1.13	1.3 (1.0–1.6)	26	0.84	1.43	1.7 (1.3–2.2)
OPA																
1	26	5.62	13.69	2.4 (1.5–3.8)	27	5.72	16.66	2.9 (1.8–4.8)	22	9.02	7.66	0.8 (0.7–1.1)	22	10.83	18.71	1.7 (1.1–2.7)
3	26	4.68	6.56	1.4 (1.0–1.9)	28	6.03	8.27	1.4 (1.0–1.8)	25	10.95	10.54	1.0 (0.8–1.1)	21	8.30	11.60	1.4 (1.1–1.7)
4	17	6.62	76.37	11.5 (3.3–39.8)	22	4.82	103.90	21.5 (7.4–62.5)	19	19.45	31.44	1.6 (1.2–2.2)	18	20.45	99.88	4.9 (1.9–12.5)
5	25	4.91	8.84	1.8 (1.3–2.6)	29	5.44	21.46	3.9 (1.9–8.0)	23	15.07	21.09	1.4 (1.0–1.9)	21	10.90	17.37	1.6 (1.0–2.5)
6A	23	13.64	117.33	8.6 (3.4–21.7)	23	21.27	158.62	7.5 (3.1–17.7)	21	42.88	82.08	1.9 (1.0–3.6)	21	43.55	289.70	6.7 (2.3–19.1)
6B	15	20.42	95.35	4.7 (1.7–13.0)	24	23.19	152.79	6.6 (3.1–14.1)	18	107.32	214.08	2.0 (1.0–3.8)	17	44.28	118.99	2.7 (1.1–6.7)
7F	26	14.34	99.31	6.9 (3.1–15.2)	27	18.31	144.37	7.9 (3.3–19.0)	23	48.97	73.09	1.5 (1.0–2.3)	20	42.94	104.17	2.4 (1.2–4.7)
9V	23	21.63	54.39	2.5 (1.3–5.0)	20	36.73	90.14	2.5 (1.3–4.8)	11	85.75	142.83	1.7 (0.6–4.3)	13	35.65	109.09	3.1 (1.3–7.0)
14	17	41.69	299.01	7.2 (2.8–18.3)	21	102.33	383.09	3.7 (1.8–8.0)	3	512.48	560.25	1.1 (0.7–1.6)	11	212.08	313.74	1.5 (1.0–2.1)
18C	20	14.17	86.93	6.1 (2.8–13.5)	24	9.44	59.61	6.3 (3.0–13.3)	23	62.48	127.17	2.0 (1.3–3.2)	17	25.25	91.62	3.6 (2.0–6.7)
19A	24	13.48	29.51	2.2 (1.3–3.8)	27	18.59	81.50	4.4 (2.1–9.2)	21	92.90	100.24	1.1 (0.7–1.6)	20	45.27	53.43	1.2 (0.8–1.7)
19F	20	10.28	23.00	2.2 (1.2–4.3)	26	8.09	49.75	6.2 (2.8–13.5)	14	30.95	32.31	1.0 (0.7–1.6)	13	27.55	71.50	2.6 (1.0–6.6)
23F	20	6.53	22.83	3.5 (1.6–7.4)	25	7.30	26.00	3.6 (1.6–7.9)	21	14.33	32.62	2.3 (1.2–4.3)	16	9.46	26.80	2.8 (1.3–6.0)

Abbreviations: PCV-13, pneumococcal conjugated vaccine; PPV-23, pneumococcal polysaccharide vaccine.
[a] Geometric mean titre ratio and 95% CI.

Table 4
Antibody titres in PPV-23-naive patients: PCV-13 (group 1) versus PPV-23 recipients (group 2)

	Antibody response at baseline			Antibody response at 4 weeks			Antibody response at 52 weeks		
	Group 1 GMT	Group 2 GMT	GMT ratio[a] (95% CI)	Group 1 GMT	Group 2 GMT	GMT ratio[a] (95% CI)	Group 1 GMT	Group 2 GMT	GMT ratio[a] (95% CI)
ELISA									
1	0.20	0.20	1.04 (0.54–1.97)	1.36	1.74	1.46 (0.70–3.04)	0.96	0.86	1.03 (0.57–1.85)
3	0.11	0.12	1.08 (0.56–2.10)	0.26	0.31	1.18 (0.73–1.89)	0.17	0.15	0.90 (0.58–1.39)
4	0.09	0.10	1.05 (0.54–2.01)	0.47	1.05	2.22 (1.10–4.46)*	0.35	0.55	1.69 (0.88–3.22)
5	1.31	1.34	1.02 (0.64–1.64)	1.65	3.30	2.34 (1.54–3.55)***	2.57	2.33	1.14 (0.79–1.64)
6A	0.83	0.95	1.15 (0.70–1.87)	1.12	2.50	2.00 (1.22–3.29)**	1.33	1.95	1.57 (1.02–2.43)*
6B	0.48	0.83	1.73 (0.86–3.48)	1.53	2.65	1.26 (0.66–2.39)	1.46	2.20	1.09 (0.69–1.75)
7F	0.61	0.79	1.30 (0.77–2.18)	2.24	6.08	2.28 (1.15–4.52)*	2.13	3.08	1.18 (0.61–2.28)
9V	0.57	0.68	1.20 (0.64–2.24)	1.53	3.00	1.85 (1.09–3.15)*	1.17	2.15	1.33 (0.86–2.06)
14	1.47	1.86	1.26 (0.70–2.27)	6.40	10.30	1.34 (0.62–2.88)	7.42	9.53	1.17 (0.56–2.48)
18C	0.60	0.63	1.05 (0.60–1.85)	2.29	3.79	1.59 (0.88–2.88)	2.01	2.20	1.18 (0.67–2.05)
19A	1.69	1.64	0.97 (0.57–1.63)	3.10	5.60	1.96 (1.19–3.22)*	2.83	3.62	1.32 (0.87–1.99)
19F	0.50	0.67	1.34 (0.71–2.53)	1.11	2.18	1.38 (0.77–2.46)	0.77	1.46	1.23 (0.75–2.03)
23F	0.58	1.04	1.78 (0.94–3.36)	1.26	2.86	1.39 (0.76–2.55)	1.16	2.15	0.91 (0.56–1.50)
OPA									
1	5.5	5.5	1.00 (0.71–1.39)	47.9	56.6	1.23 (0.53–2.88)	14.3	15.3	1.20 (0.61–2.34)
3	4.5	5.9	1.33 (0.97–1.82)	27.4	16.0	0.47 (0.25–0.90)*	6.4	7.9	0.98 (0.65–1.48)
4	7.2	5.5	0.76 (0.37–1.53)	388.6	370.0	1.56 (0.30–8.08)	107.2	113.9	1.87 (0.37–9.51)
5	4.6	5.1	1.12 (0.86–1.45)	20.7	70.4	3.59 (1.47–8.75)**	11.9	19.6	2.19 (0.95–5.07)
6A	11.4	26.9	2.37 (0.92–6.09)	233.5	708.7	1.59 (0.47–5.41)	107.0	141.9	0.87 (0.24–3.08)
6B	16.1	31.0	1.93 (0.58–6.37)	454.7	897.6	1.44 (0.34–6.05)	126.8	218.5	1.41 (0.40–4.97)
7F	12.1	23.9	1.97 (0.80–4.88)	262.7	589.3	1.45 (0.45–4.65)	104.2	142.2	1.14 (0.35–3.72)
9V	41.3	29.1	0.70 (0.21–2.34)	322.5	415.9	1.10 (0.30–4.07)	64.4	77.9	0.98 (0.37–2.56)
14	38.4	98.0	2.55 (0.78–8.33)	464.8	753.8	0.54 (0.14–2.16)	223.3	402.2	0.52 (0.16–1.71)
18C	13.0	11.4	0.88 (0.37–2.07)	187.3	179.7	0.82 (0.24–2.77)	76.8	66.1	1.03 (0.35–3.05)
19A	19.4	17.8	0.92 (0.44–1.93)	114.6	128.7	1.30 (0.53–3.22)	27.5	72.6	2.00 (0.78–5.12)
19F	12.9	11.3	0.87 (0.40–1.93)	118.5	153.5	1.46 (0.42–5.14)	20.9	46.0	2.75 (0.95–7.98)
23F	7.5	7.9	1.05 (0.50–2.20)	65.4	71.4	0.65 (0.16–2.54)	25.9	30.3	1.02 (0.33–3.11)

Abbreviations: PCV-13, pneumococcal conjugated vaccine; PPV-23, pneumococcal polysaccharide vaccine.
*p <0.05; **p <0.01; ***p <0.001.
[a] Geometric mean titre ratio and 95% CI.

Table 5
Baseline antibody titres in PCV-13 recipients: PPV-23-naive (group 2) versus PPV-23-pre-vaccinated (groups 3 + 4)

	Antibody response at baseline			Antibody response at 4 weeks			Antibody response at 52 weeks		
	Group 2 GMT	Group 3+4 GMT	GMT ratio[a] (95% CI)	Group 2 GMT	Group 3+4 GMT	GMT ratio[a] (95% CI)	Group 2 GMT	Group 3+4 GMT	GMT ratio[a] (95% CI)
ELISA									
1	0.20	0.53	0.38 (0.20–0.73)**	1.74	1.02	4.75 (2.84–7.93)***	0.86	1.02	2.61 (1.69–4.04)***
3	0.12	0.14	0.90 (0.45–1.81)	0.31	0.21	1.68 (1.21–2.33)**	0.15	0.16	0.99 (0.69–1.43)
4	0.10	0.18	0.53 (0.29–0.96)*	1.05	0.53	3.89 (2.27–6.66)***	0.55	0.54	2.72 (1.62–4.58)***
5	1.34	1.40	0.96 (0.57–1.61)	3.30	1.97	2.05 (1.45–2.91)***	2.33	2.12	1.64 (1.23–2.19)**
6A	0.95	0.70	1.37 (0.84–2.22)	2.50	1.64	1.24 (0.73–2.09)	1.95	1.74	1.27 (0.78–2.07)
6B	0.83	0.68	1.22 (0.65–2.30)	2.65	1.76	1.96 (1.16–3.29)*	2.20	1.83	1.69 (1.08–2.66)*
7F	0.79	0.99	0.79 (0.45–1.40)	6.08	1.87	4.44 (2.64–7.45)***	3.08	1.92	2.44 (1.55–3.85)***
9V	0.68	0.84	0.81 (0.45–1.45)	3.00	1.62	2.63 (1.72–4.01)***	2.15	1.62	2.00 (1.40–2.86)***
14	1.86	1.95	0.95 (0.56–1.64)	10.30	4.10	2.89 (1.74–4.80)***	9.53	3.88	3.29 (2.07–5.23)***
18C	0.63	1.08	0.59 (0.34–1.02)	3.79	2.37	2.66 (1.67–4.24)***	2.20	2.13	2.22 (1.46–3.36)***
19A	1.64	1.75	0.94 (0.52–1.69)	5.60	3.49	1.84 (1.18–2.85)**	3.62	3.42	1.44 (1.01–2.03)*
19F	0.67	0.78	0.85 (0.45–1.63)	2.18	1.25	1.92 (1.23–3.00)**	1.46	1.66	1.39 (0.93–2.09)
23F	1.04	0.72	1.45 (0.82–2.54)	2.86	1.29	1.93 (1.24–3.01)***	2.15	1.26	1.44 (1.04–2.00)*
OPA									
1	5.5	9.9	0.56 (0.38–0.83)**	56.6	26.0	4.07 (2.14–7.77)***	15.3	11.6	2.40 (1.44–4.02)**
3	5.9	8.5	0.70 (0.45–1.09)	16.0	14.4	1.73 (1.08–2.79)***	7.9	11.1	1.20 (0.90–1.60)
4	5.5	25.2	0.22 (0.09–0.53)**	370.0	236.8	9.63 (2.79–33.26)*	113.9	66.7	7.78 (2.72–22.26)***
5	5.1	12.1	0.43 (0.25–0.72)*	70.4	42.9	4.01 (1.88–8.56)***	19.6	19.6	2.65 (1.37–5.13)**
6A	26.9	39.8	0.68 (0.27–1.68)	708.7	431.2	3.22 (1.01–10.23)	141.9	182.2	2.09 (0.72–6.11)
6B	31.0	74.8	0.41 (0.14–1.18)	897.6	381.1	5.00 (1.57–15.89)**	218.5	174.6	2.86 (1.14–7.14)*
7F	23.9	47.8	0.50 (0.21–1.21)	589.3	246.3	5.63 (2.22–14.28)***	142.2	96.1	4.21 (1.80–9.85)**
9V	29.1	50.4	0.58 (0.18–1.85)	415.9	248.1	2.06 (0.59–7.20)	77.9	119.8	1.06 (0.43–2.64)
14	98.0	118.9	0.82 (0.26–2.60)	753.8	250.4	4.69 (1.44–15.26)*	402.2	249.2	2.70 (1.03–7.06)*
18C	11.4	39.6	0.29 (0.12–0.68)**	179.7	163.4	3.59 (1.51–8.51)**	66.1	119.1	2.43 (1.15–5.13)*
19A	17.8	47.8	0.37 (0.19–0.74)**	128.7	148.3	2.85 (1.39–5.82)**	72.6	79.3	3.89 (1.96–7.70)***
19F	11.3	22.1	0.51 (0.24–1.07)	153.5	97.7	4.35 (1.51–12.52)**	46.0	57.5	3.80 (1.49–9.68)**
23F	7.9	12.1	0.65 (0.32–1.31)	71.4	53.2	1.92 (0.67–5.49)	30.3	42.1	1.42 (0.59–3.43)

Abbreviations: PCV-13, pneumococcal conjugated vaccine; PPV-23, pneumococcal polysaccharide vaccine.
*p <0.05; **p <0.01; ***p <0.001.
[a] Geometric mean titre ratio and 95% confidence interval.

pneumonia incidence was 7.1 %, with no differences among the treatment groups. Nine (5.8 %) patients underwent transplantation, and four (2.6 %) were lost to follow up.

Adverse effects

Adverse effects are summarized in the Supplementary material (Table S1). Local adverse effects, especially pain and decreased mobility, occurred in up to one-fifth of the patients, mainly during the first 3 days after vaccination. Local adverse effects, especially pain, tended to be more common in the PCV-13 groups than in the PPV-23 group. Fatigue, muscle aches and headache were common in all patient groups.

Discussion

The current longitudinal semi-experimental phase IV trial benchmarks antibody response after vaccination with either PPV-23 or PCV-13 in 155 patients with ESRD treated with chronic haemodialysis. In non-PPV-23-pre-vaccinated patients, both PPV-23 and PCV-13 induced a significant and durable antibody response for 12 of the 13 antigens. Four-week antibody titres were higher in PCV-13-vaccinated patients than in PPV-23-vaccinated patients, but these differences grossly disappeared after 1 year. Non-PPV-23-pre-vaccinated patients vaccinated with PCV-13 tended to have a lower mortality than the other arms of the study. This trial was, however, not designed to permit any conclusions on mortality. In PPV-23-pre-vaccinated patients, PCV-13 induced an immune response after 1 month, that partly waned after 1 year to values that were only marginally higher than baseline values. Immune response after PCV-13 was weaker in PPV-23-pre-vaccinated than in non-PPV-23-pre-vaccinated patients. Local adverse effects, especially pain, tended to be more frequent after PCV-13 than after PPV-23. Despite vaccination against pneumococci in all patients included in this trial, the 1-year hospitalization rate for pneumonia was 7.1% and 1-year mortality was 17.4% in populations with ESRD.

The long-lasting antibody response in non-PPV-23-pre-vaccinated patients observed in this study clearly supports the guidelines recommending universal pneumococcal vaccination in patients with ESRD [18–21]. Although PCV-13 seems to be more immunogenic after 1 month than PPV-23 in non-PPV-23-immunized patients, the data in this study do not permit firm conclusions on the preferred vaccination strategy. A future study in non-PPV-23-pre-vaccinated patients that compares the effect of a single PCV-13 vaccination with a PCV-13 prime and PPV-23 boost strategy, as proposed by American, French and Spanish Guidelines, would be informative [19–21]. The weaker immune response in PPV-23-pre-vaccinated patients may be caused by the higher dialysis vintage in the PPV-23-pre-vaccinated groups, or by an inhibitory effect of previous PPV-23 vaccination on the (amnestic) immune response after PCV-13, as has been previously described [22]. This study does not provide information on the usefulness of booster vaccination. The differences in baseline OPA titres suggest at least some long-lasting protective antibodies after vaccination with PPV-23.

The trial has several shortcomings. First, the trial was not powered to detect an impact of pneumococcal vaccination with either PPV-23 or PCV-13 vaccine on invasive pneumococcal disease and mortality in this population, but only provides data on secondary, serological outcome measurements. Second, the trial generated a large amount of serological data without clear guidance on how to interpret them. In children, there seems to be a good correlation between high ELISA antibody titres, high OPA *in vitro* opsonophagocytic activity, and protection against experimental challenge in mice. This correlation and the interpretation of serological data are less well established in the elderly and immunocompromised patients [1,23]. Moreover, serological cut-

offs that define clinical significant protection are poorly defined. Third, where the trial design favours the generation of a large set of comparative data in a relatively small population, it lacks the methodological power of prospective, randomized vaccination trials. Fourth, group 3 and 4 patients have a slightly higher dialysis vintage, and represent consequently a group of patients that are likely to have an intrinsically slightly worse prognosis than group 1 and 2 patients. However, up to now, the data generated in this study provide the best available prospective data on pneumococcal vaccination in patients with ESRD treated with haemodialysis.

Transparency declaration

The study is investigator-driven. Study design, data collection, data analysis and publication are the sole responsibility of the investigators. Pfizer provided the vaccines free of charge and bore the costs for quantitative and qualitative antibody response assessment. The investigators did not receive any compensation for this trial except for costs directly related to the study.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cmi.2017.05.016.

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