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Immunogenicity of the 13-Valent Pneumococcal Conjugate Vaccine in Older Adults With and Without Comorbidities in the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA)

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Background. In the randomized controlled Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA), the efficacy of the 13-valent pneumococcal conjugate vaccine (PCV13) against first episodes of vaccine-type community-acquired pneumonia in adults aged ≥65 years was 46%. The long-term immunogenicity of PCV13 in pneumococcal vaccine–naive older adults was investigated as part of CAPiTA.

Methods. We determined the immune responses to PCV13 before and at 1, 12, and 24 months after vaccination in 1006 PCV13 recipients and 1005 controls with 3 age-stratified study participant cohorts. PCV13 serotype-specific opsonophagocytic activity (OPA) titers and immunoglobulin G (IgG) concentrations were determined.

Results. Sample collection completeness was at least 93.4% at each time point. In all 3 age categories, a single dose of PCV13 elicited OPA titers and IgG concentrations for all 13 serotypes that were significantly higher than baseline and the corresponding responses in the placebo group at all time points. In the eldest subjects (≥80 years of age at vaccination), OPA titers and IgG concentrations remained above baseline and there was no apparent difference in OPA titers and IgG concentrations between those with self-reported comorbidities and healthy older adults. However, the study was not powered to determine statistical significance between different age and comorbidity groups, and thus these results are exploratory.

Conclusions. In immunocompetent adults ≥65 years of age, PCV13 elicits significant increases in OPA titers and IgG concentrations that persist 2 years postvaccination for all 13 serotypes, regardless of age and comorbidity.

Clinical Trials Registration. NCT00744263

Keywords. vaccine immunogenicity; PCV13; adult; RCT; OPA.

Streptococcus pneumoniae is a significant cause of community-acquired pneumonia (CAP) in older adults, resulting in notable mortality and morbidity [1, 2]. Apart from age, those with certain medical conditions are at increased risk for developing pneumococcal infections with severe disease course and complications.

Immunological protection against pneumococcal disease is mediated through opsonophagocytic antibodies directed against bacterial capsular polysaccharides that define the pneumococcal serotypes [3]. Pneumococcal vaccination strategies aim to achieve immunological protection through vaccination with pneumococcal polysaccharides. Vaccines composed of purified capsular polysaccharides (PPVs) have been available for decades and used in adults worldwide. PPVs appear to be effective against invasive pneumococcal disease (IPD) in adults, but their efficacy against noninvasive pneumonia remains debatable [4–6].

Also, there are reports on possible hyporesponsiveness after receiving PPV to later administered pneumococcal conjugate vaccines (PCVs) [7–11]. In older adults this is further complicated by immunosenescence resulting in lower responses to both PPV and PCV [9, 12] and vaccine effectiveness of PPV decreasing with age and waning over time [13].

In 2000, the first PCV was licensed, conjugating capsular polysaccharides of the 7 most prevalent pneumococcal serotypes causing IPD in US children to a nontoxic diphtheria toxin cross-reactive material 197 (CRM_{197}) protein. This 7-valent PCV (PCV7) had limited coverage for pneumococcal serotypes causing IPD in adults. In 2009, the 13-valent PCV (PCV13)

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was introduced with better coverage against pneumococcal disease in all age groups. In adults 60–64 years of age, PCV13 was found to induce a greater functional immune response than the 23-valent PPV, suggesting that PCVs offer immunological advantages over PPVs for prevention of vaccine-type (VT) pneumococcal infection in adults [14]. It is unknown how long immune responses after PCV13 last, but a recent study in adults aged 50–59 years shows that antibody titers were maintained for at least 5 years postvaccination for 12 of the 13 vaccine serotypes [15]. In previous studies, no major differences in immunological responses to PCVs were observed between older adults suffering from common comorbidities such as diabetes mellitus or chronic lung disease as compared to healthy older adults [16–18].

The Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA), a randomized, double-blind clinical trial in 84 496 participants aged ≥65 years in the Netherlands, demonstrated the efficacy of PCV13 against first episodes of VT-CAP and first episodes of VT-IPD [18]. Within this study we have assessed the long-term immune responses to PCV13 compared with placebo up to 24 months postvaccination within a subset of 2011 vaccine-naive adults in different age and comorbidity groups.

METHODS

Immunogenicity data were collected as a substudy within CAPiTA. The study was a collaboration between University Medical Center Utrecht (UMCU) and the study sponsor, Wyeth, a Pfizer company. Study design and primary and secondary endpoints including safety data were previously published [18, 19].

The study was conducted according to a written protocol and in compliance with Good Clinical Practice, and approved by the Central Committee on Research Involving Human Subjects and Ministry of Health, Welfare, and Sport in the Netherlands. The UMCU, Julius Clinical (an academic research organization affiliated with UMCU), and the Linnaeus Institute (a research organization of the Spaarne Hospital in Hoofddorp) conducted the immunogenicity substudy and gathered all data. The sponsor performed data management as well as immunogenicity and statistical analysis. Confidentiality agreements were in place between the sponsor, Spaarne Hospital, and UMCU, which allowed full access to all data and right to publish.

Study Design and Population

The study was a parallel-group, randomized, placebo-controlled, double-blind trial [19]. Use of a placebo was appropriate because no pneumococcal vaccine is recommended in the Netherlands for routine use in adults [19–21]. PPV23 is only advised in specific risk groups (eg, people suffering from asplenia, sickle-cell anemia, or liquor leakage after the age of 2 years), resulting in <1% of older adults having received PPV23 [19–21]. For infants, PCV7 was introduced in the national immunization program for children in June 2006 and was recommended for all infants born on or after 1 April 2006 as a 3 + 1 dose series at 2, 3, and 4 months of age with a booster at 11 months [22] without a catch-up campaign. In 2011, PCV7 was replaced by the 10-valent pneumococcal *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV10) for all infants born on or after 1 March 2011 at age 2, 4, and 11 months.

A subset of 2011 subjects was enrolled in a single region in the Netherlands for the immunogenicity substudy. Subjects were aged ≥65 years and enrolled between 15 September 2008 and 20 March 2009 at home visits. Eligibility criteria were no previous pneumococcal vaccination and immunocompetence evaluated by self-report. All subjects with immunocompromising conditions were excluded from the study. All subjects provided written informed consent. Full details of the eligibility criteria are provided in the Supplementary Materials.

Subjects were vaccinated at home visit 1 (baseline) and followed for 2 years through home visits to collect blood samples at baseline and at 1 month (day 29–43), 12 months, and 24 months postvaccination (Supplementary Figure 1). All visits were performed by trained study personnel. Smoking status and comorbidities such as asthma, diabetes mellitus, heart disease, liver disease, lung disease, and splenectomy were reported by subjects at baseline and documented on a prespecified list (Supplementary Materials).

Investigational Products

Subjects were randomly assigned in a 1:1 ratio to receive PCV13 or placebo by intramuscular injection in the right deltoid. PCV13 contains capsular polysaccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to a CRM_{197} protein. The vaccine contains 2.2 μg of each polysaccharide, except for 4.4 μg of serotype 6B, with 5.0 mM succinate buffer, 0.85% sodium chloride, 0.02% polysorbate 80, and 0.125 mg aluminum as aluminum phosphate per 0.5-mL dose. The placebo contained 5.0 mM succinate buffer, 0.15 M sodium chloride, 0.02% polysorbate 80, and 0.125 mg aluminum as aluminum phosphate per 0.5-mL dose and was identical in appearance to PCV13.

Immunogenicity Analyses

Serum opsonophagocytic activity (OPA) titers for the 13 pneumococcal VTs were determined for all subjects and each blood sample to ascertain the concentration of functional anticapsular antibodies (antibody titer). This was done using a microcolony assay with a titer killing 50% of the bacteria in the assay as previously described [23–25]. OPA titers above the lower limit of quantitation (LLOQ) were considered accurate and their quantified values reported. OPA values below LLOQ were set to 0.5 × LLOQ for purposes of summary and analysis.

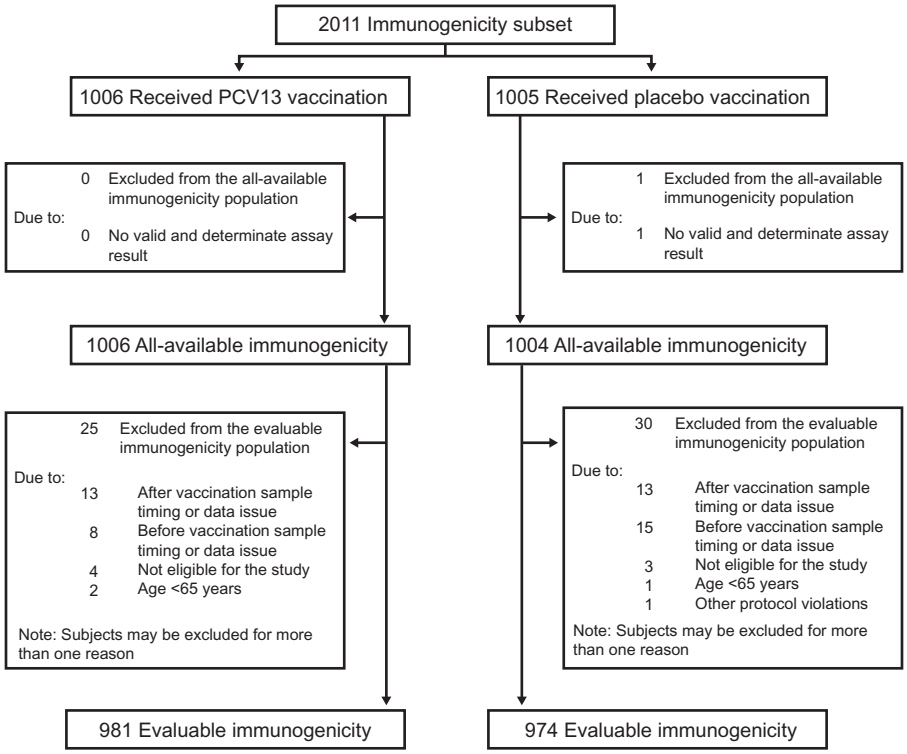

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram. Abbreviation: PCV13, 13-valent pneumococcal conjugate vaccine.

Enzyme-linked immunosorbent assay was used to determine the concentration of VT anticapsular pneumococcal binding immunoglobulin G (IgG), expressed as micrograms per milliliter as described elsewhere [26–28]. IgG values below the LLOQ were set to 0.5 × lower limit of detection (LOD) for purposes of summary and analysis.

Statistical Analyses

Within each vaccine group and for each serotype, OPA geometric mean antibody titers (GMTs) were calculated at all time points (baseline and 1, 12, and 24 months postvaccination) with 2-sided 95% confidence intervals (CIs). As post hoc analysis, the proportion of subjects achieving a ≥4-fold increase in OPA titer was assessed within each vaccine group and for each serotype. Although there is no consensus for a clinically meaningful, empirically predefined level of protection in adults, we considered subjects with OPA titers at baseline below LLOQ, but above LOD a responder when achieving a ≥4-fold increase in LLOQ. Subjects with OPA titers at baseline below LOD were considered a responder when achieving a ≥4-fold increase in LOD.

Similar analyses were done for IgG concentrations using geometric means of the IgG antibody concentrations (GMCs). For IgG, subjects achieving a ≥4-fold increase in IgG concentration with a minimal level of 1.00 μg/mL were considered responders. The minimum value of 1.00 mg/mL is a convenient cutoff that lies well above the 0.35 mg/mL used in children. It has not been tested in clinical studies.

Differences were considered significant if the nominal 95% CI excluded 0 for an endpoint of a difference between the compared groups (or 1 for an endpoint of a ratio of the compared groups)

Table 1. Baseline Characteristics and Patient-Reported Comorbidities

Characteristic	PCV13 (n = 981)	Placebo (n = 974)
Age at vaccination, y		
Mean (SD)	72.6 (5.5)	72.5 (5.6)
Range	65.1–92.3	65.0–94.0
65–69	40.3 (395)	42.4 (413)
70–79	48.3 (474)	45.9 (447)
≥80	11.4 (112)	11.7 (114)
Male sex	53.0 (520)	55.7 (543)
White race	98.9 (970)	98.7 (961)
Current smoker	7.7 (76)	11.2 (109)
Patient-reported comorbidities		
Any	42.8 (420)	39.4 (384)
Heart disease[a]	23.2 (228)	22.2 (216)
Diabetes mellitus[a]	11.9 (117)	11.6 (113)
Insulin use	2.2 (22)	2.3 (22)
No insulin use	9.7 (95)	9.3 (91)
Lung disease[a]	10.4 (102)	10.1 (98)
Asthma[a]	5.1 (50)	4.6 (45)
Liver disease[a]	0.5 (5)	0.4 (4)
Splenectomy[a]	0.1 (1)	0.1 (1)

Data are presented as % (No.) unless otherwise indicated.

Abbreviations: PCV13, 13-valent pneumococcal conjugate vaccine; SD, standard deviation.

[a]Not mutually exclusive.

without adjusting for multiplicity due to multiple endpoints, time points, and comparisons.

RESULTS

Of the 2011 subjects enrolled in the immunogenicity substudy, 1006 received PCV13 and 1005 received placebo. Less than 3% (n = 56 [2.8%]) of the subjects were excluded from analyses, evenly divided over both groups (Figure 1). The most common reason for exclusion was absence of a blood sample within the required time period. At each collection point, at least 93.4% of samples were collected within the required time period. Missing values were well balanced between the 2 groups. Discontinuation rates over the course of the study were 11.4% (n = 115) in PCV13 recipients and 12.1% (n = 122) in the placebo group. Discontinuation was mainly due to death (n = 142 [7.1%]).

Average age at vaccination was 72.5 years; 11.6% (n = 226) of the subjects were ≥80 years of age. Baseline characteristics as well as patient-reported comorbidities were well balanced between the 2 groups (Table 1). Heart disease was the most commonly reported comorbidity (n = 444 [22.7%]). There were no differences in age and comorbidity distribution between this subset and other subjects within CAPiTA [18].

Opsonophagocytic Activity

Before vaccination, the OPA GMTs were similar in both groups (Table 2). The OPA GMTs in the placebo group remained constant over time (Figure 2). The OPA GMTs increased in PCV13 recipients 1 month postvaccination and decreased at 12 and 24 months after vaccination, but remained above baseline for all serotypes (Table 2). The OPA GMTs of all 13 serotypes were statistically higher than baseline and the corresponding

Table 2. Pneumococcal Opsonophagocytic Activity Geometric Mean Antibody Titers per Serotype Before and After Vaccination With 13-Valent Pneumococcal Conjugate Vaccine

Serotype	Vaccine Group	Baseline			1 Month				12 Months				24 Months			
		No.[a]	GMT[b]	(95% CI[c])	No.[a]	GMT[b]	(95% CI[c])	GMFR[d]	No.[a]	GMT[b]	(95% CI[c])	GMFR[d]	No.[a]	GMT[b]	(95% CI[c])	GMFR[d]
1	PCV13	975	10	(9.8–10.4)	965	97	(87.7–107.6)	10	941	32	(29.1–34.7)	3	924	22	(20.5–24.0)	2
	Placebo	968	10	(9.7–10.3)	957	10	(9.7–10.2)	1	936	10	(9.7–10.3)	1	913	10	(9.5–10.1)	1
3	PCV13	966	8	(7.5–8.3)	948	59	(54.0–64.8)	7	928	19	(17.4–20.6)	2	915	13	(12.0–13.9)	1
	Placebo	962	8	(7.3–8.0)	942	8	(7.5–8.3)	1	924	8	(7.3–8.0)	1	904	7	(7.0–7.7)	1
4	PCV13	946	20	(18.4–22.3)	953	1352	(1210.7–1510.2)	66	920	308	(270.5–350.5)	14	904	171	(149.3–196.0)	8
	Placebo	939	22	(19.7–24.1)	916	22	(19.5–23.9)	1	884	22	(19.9–24.6)	1	873	22	(19.3–23.9)	1
5	PCV13	967	16	(15.2–15.9)	938	104	(94.0–115.8)	7	938	44	(40.5–48.2)	3	918	37	(34.3–40.2)	2
	Placebo	962	16	(15.4–16.1)	941	16	(15.5–16.3)	1	923	16	(15.3–16.0)	1	905	16	(15.3–16.0)	1
6A	PCV13	910	64	(57.3–70.8)	963	1766	(1587.8–1964.5)	27	921	689	(618.7–766.9)	10	881	382	(342.2–426.1)	6
	Placebo	887	69	(61.8–77.1)	885	72	(64.3–80.2)	1	873	79	(70.3–88.4)	1	849	59	(52.7–65.2)	1
6B	PCV13	885	99	(87.0–111.6)	943	1816	(1623.6–2030.3)	18	912	661	(588.8–743.1)	6	887	433	(384.5–488.6)	4
	Placebo	894	97	(85.3–109.8)	871	96	(84.4–108.9)	1	842	92	(81.0–104.4)	1	831	87	(76.4–98.3)	1
7F	PCV13	936	166	(156.6–176.2)	963	1753	(1615.5–1901.1)	10	939	670	(620.2–723.0)	4	916	416	(386.6–446.9)	2
	Placebo	936	176	(165.8–186.9)	937	173	(163.3–183.5)	1	919	179	(168.9–190.7)	1	888	164	(155.4–173.9)	1
9V	PCV13	952	240	(228.1–251.7)	944	1089	(996.5–1190.1)	5	925	536	(497.3–577.7)	2	897	370	(346.1–395.9)	2
	Placebo	940	244	(232.4–257.2)	932	245	(232.9–257.6)	1	908	247	(235.0–260.4)	1	879	239	(227.2–250.8)	1
14	PCV13	952	126	(111.5–141.5)	949	988	(894.4–1090.8)	8	932	537	(487.5–591.9)	4	915	391	(352.2–433.2)	3
	Placebo	939	134	(119.6–151.1)	930	135	(120.4–151.8)	1	912	137	(121.9–154.0)	1	881	124	(110.3–139.9)	1
18C	PCV13	963	45	(40.4–49.2)	962	1482	(1318.2–1666.5)	33	930	438	(388.8–493.9)	10	916	301	(267.0–340.0)	7
	Placebo	953	44	(39.9–48.9)	939	43	(38.7–47.5)	1	919	45	(40.3–49.7)	1	898	43	(38.5–47.4)	1
19A	PCV13	969	30	(27.8–33.2)	966	702	(634.5–777.3)	23	940	229	(207.5–252.4)	8	918	163	(147.1–179.9)	5
	Placebo	966	28	(25.9–30.9)	958	28	(25.3–30.2)	1	932	26	(23.7–28.2)	1	907	26	(23.6–28.0)	1
19F	PCV13	958	38	(35.5–40.3)	929	578	(513.4–650.4)	15	922	182	(163.9–203.2)	5	902	128	(115.4–141.7)	3
	Placebo	955	38	(35.7–41.0)	941	38	(35.9–41.1)	1	910	39	(36.5–41.9)	1	900	37	(34.8–39.8)	1
23F	PCV13	955	13	(12.2–14.7)	949	322	(277.3–373.2)	23	924	104	(90.1–119.8)	8	910	70	(60.9–80.3)	5
	Placebo	935	14	(12.7–15.4)	930	14	(12.4–15.1)	1	908	14	(12.5–15.3)	1	894	13	(11.8–14.3)	1

Opsonophagocytic activity values below the lower limit of quantitation (LLOQ) were set to 0.5 × lower limit of detection for purposes of summary and analysis. LLOQs are as follows: serotype 1, 18; serotype 3, 12; serotype 4, 21; serotype 5, 29; serotype 6A, 37; serotype 6B, 43; serotype 7F, 210; serotype 9V, 345; serotype 14, 35; serotype 18C, 31; serotype 19A, 18; serotype 19F, 48; serotype 23F, 13.

Abbreviations: CI, confidence interval; GMFR, geometric mean fold rise; GMT, geometric mean titer; PCV13, 13-valent pneumococcal conjugate vaccine.

[a]No. indicates number of subjects with valid and determinate assay results for the specified serotype at the given visit.

[b]GMTs were calculated using all subjects with available data for the specified blood draw.

[c]CIs are back-transformations of a CI based on the Student *t* distribution for the mean logarithm of the titers.

[d]GMFRs were calculated using all subjects with available data from both the before-vaccination and after-vaccination blood draws.

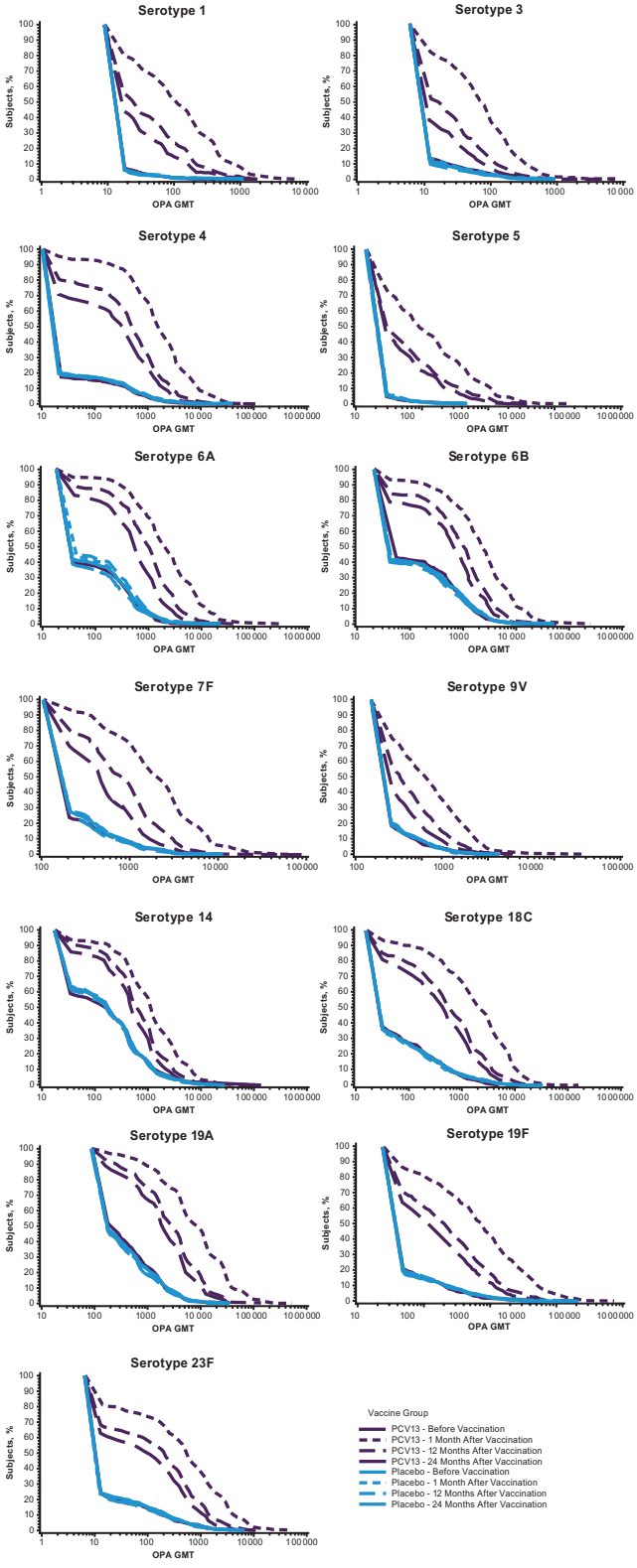

Figure 2. Reverse cumulative distribution curves of opsonophagocytic activity (OPA) geometric mean antibody titers (GMT) per 13-valent pneumococcal conjugate vaccine (PCV13) serotype. OPA values below the lower limit of quantitation (LLOQ) were set to 0.5 × LLOQ for purposes of summary and analysis. LLOQs: serotype 1, 18; serotype 3, 12; serotype 4, 21; serotype 5, 29; serotype 6A, 37; serotype 6B, 43; serotype 7F, 210; serotype 9V, 345; serotype 14, 35; serotype 18C, 31; serotype 19A, 18; serotype 19F, 48; serotype 23F, 13.

values in the placebo group at each postvaccination time point. The largest effects of PCV13 at 24 months postvaccination were observed for serotypes 4 and 18C (GMT >6-fold higher than baseline) and the smallest effects, for serotypes 3 and 9V (GMT <2-fold higher than baseline) (Table 2). The decline in OPA GMTs was more pronounced in the first year than the second year postvaccination (Figure 2).

The proportion of subjects who achieved a ≥4-fold increase in OPA titer 1 month postvaccination varied between 53.2% for serotype 14 to 86.5% for serotype 4 (Supplementary Table 1).

There was no difference between male and female subjects (data not shown).

Immunoglobulin G Antibodies

The IgG GMCs showed a similar pattern as the OPA GMTs (Table 3). IgG GMCs in the placebo group remained constant or decreased slightly (serotypes 3, 9V, 19A, 19F, and 23F), though not significantly. In PCV13 recipients, the IgG GMCs of all 13 serotypes increased after vaccination and declined after 1 month postvaccination. The largest difference at 24 months postvaccination was observed for serotypes 4 and 18C (GMC >4-fold higher than baseline) and the smallest for serotypes 3, 5, 6A, 6B, and 23F (GMC <2-fold higher than baseline). IgG GMCs in PCV13 recipients remained both above baseline and corresponding placebo levels for 2 years postvaccination, which was statically significant at each postvaccination time point.

In PCV13 recipients, the proportion of subjects reaching a ≥4-fold increase in IgG concentration with a minimal level of 1.00 μg/mL 1 month postvaccination varied between 32.7% for serotype 3 to 75.8% for serotype 4 (Supplementary Table 2).

There was no difference between male and female subjects (data not shown).

Impact of Age

In the eldest PCV13 recipients (≥80 years of age at vaccination; n = 112 [11.4%]) postvaccination OPA GMTs were generally lower than in younger subjects, most obviously for serotypes 6A, 6B, 9V, 14, 18C, and 23F (Table 4). In addition, postvaccination fold increases in OPA GMTs in PCV13 recipients ≥80 years of age at vaccination were generally lower than in younger subjects, most obviously for serotypes 6B, 18C, 19A, and 23F (Table 4). For serotype 14, there was a higher fold increase in PCV13 recipients ≥80 years of age at vaccination compared to younger age groups, though the resulting OPA at 12 and 24 months remained lower than in other age groups (Table 4).

OPA GMTs of PCV13 recipients ≥80 years of age at vaccination remained above both baseline and the corresponding GMTs in the placebo group during the 2-year study period. The proportion of subjects achieving a ≥4-fold increase in OPA titer 1 month postvaccination appeared to be lower in PCV13 recipients ≥80 years of age at vaccination (Supplementary Table 3).

Table 3. Pneumococcal Immunoglobulin G Geometric Mean Antibody Concentrations per Serotype Before and After Vaccination With 13-Valent Pneumococcal Conjugate Vaccine

Serotype	Vaccine Group	Baseline			1 Month				12 Months				24 Months			
		No.[a]	GMC[b]	(95% CI[c])	No.[a]	GMC[b]	(95% CI[c])	GMFR[d]	No.[a]	GMC[b]	(95% CI[c])	GMFR[d]	No.[a]	GMC[b]	(95% CI[c])	GMFR[d]
1	PCV13	943	0.48	(.45–.52)	969	3.62	(3.29–3.99)	7.60	948	1.84	(1.67–2.02)	3.84	924	1.36	(1.23–1.50)	2.85
	Placebo	933	0.50	(.46–.54)	935	0.48	(.45–.53)	0.97	908	0.43	(.40–.47)	0.88	870	0.34	(.31–.37)	0.69
3	PCV13	940	0.44	(.41–.48)	965	1.35	(1.25–1.45)	3.02	921	0.70	(.65–.76)	1.56	902	0.53	(.49–.57)	1.18
	Placebo	941	0.47	(.43–.50)	936	0.45	(.42–.49)	0.97	888	0.42	(.39–.46)	0.91	861	0.34	(.31–.37)	0.73
4	PCV13	916	0.27	(.25–.30)	964	3.22	(2.93–3.55)	12.12	945	1.42	(1.30–1.55)	5.31	922	1.16	(1.06–1.27)	4.29
	Placebo	935	0.30	(.27–.32)	933	0.29	(.27–.32)	1.00	910	0.28	(.26–.31)	0.96	882	0.26	(.24–.28)	0.90
5	PCV13	979	2.15	(2.04–2.27)	972	7.02	(6.45–7.63)	3.25	953	4.12	(3.83–4.42)	1.91	932	3.67	(3.41–3.92)	1.69
	Placebo	972	2.24	(2.11–2.37)	965	2.19	(2.06–2.32)	0.98	942	2.14	(2.01–2.27)	0.96	918	2.07	(1.94–2.20)	0.92
6A	PCV13	978	2.15	(2.03–2.27)	961	7.88	(7.22–8.60)	3.66	952	4.41	(4.09–4.74)	2.05	930	3.72	(3.43–4.00)	1.73
	Placebo	972	2.34	(2.20–2.48)	964	2.29	(2.16–2.44)	0.98	938	2.18	(2.04–2.32)	0.93	912	1.92	(1.79–2.05)	0.82
6B	PCV13	979	2.18	(2.04–2.33)	960	9.30	(8.50–10.18)	4.17	948	5.35	(4.94–5.79)	2.43	925	4.29	(3.97–4.64)	1.94
	Placebo	971	2.34	(2.19–2.50)	965	2.26	(2.11–2.42)	0.97	940	2.31	(2.15–2.48)	0.98	915	1.97	(1.83–2.11)	0.83
7F	PCV13	971	0.93	(.86–.99)	964	10.19	(9.30–11.17)	11.01	945	4.44	(4.10–4.82)	4.78	927	3.48	(3.21–3.79)	3.78
	Placebo	966	1.04	(.97–1.12)	959	1.05	(.98–1.13)	1.00	939	1.01	(.94–1.10)	0.98	918	0.92	(.85–.99)	0.88
9V	PCV13	978	1.21	(1.14–1.28)	961	7.57	(6.98–8.21)	6.19	949	3.91	(3.62–4.21)	3.21	930	3.19	(2.96–3.44)	2.62
	Placebo	974	1.26	(1.18–1.34)	963	1.24	(1.16–1.33)	0.99	941	1.13	(1.06–1.21)	0.90	917	1.03	(.96–1.10)	0.81
14	PCV13	977	1.97	(1.82–2.14)	969	11.99	(10.92–13.16)	6.08	947	7.66	(7.01–8.37)	3.84	928	6.08	(5.56–6.64)	3.03
	Placebo	973	2.00	(1.84–2.18)	962	1.98	(1.81–2.15)	0.99	942	1.89	(1.74–2.06)	0.94	917	1.73	(1.60–1.89)	0.85
18C	PCV13	974	0.96	(.89–1.03)	968	12.21	(11.15–13.36)	12.73	939	5.54	(5.10–6.02)	5.71	925	4.38	(4.04–4.74)	4.51
	Placebo	972	1.01	(.93–1.08)	963	1.01	(.93–1.09)	1.01	940	0.97	(.89–1.05)	0.96	916	0.92	(.85–1.00)	0.91
19A	PCV13	981	3.45	(3.26–3.66)	971	18.07	(16.57–19.70)	5.18	953	8.62	(8.01–9.28)	2.48	932	7.33	(6.76–7.89)	2.10
	Placebo	973	3.41	(3.21–3.63)	965	3.42	(3.21–3.63)	1.00	942	3.16	(2.97–3.37)	0.93	918	2.85	(2.66–3.04)	0.84
19F	PCV13	955	1.32	(1.23–1.42)	968	7.23	(6.54–7.98)	5.58	948	3.67	(3.36–4.02)	2.86	926	2.76	(2.51–3.01)	2.14
	Placebo	938	1.34	(1.24–1.45)	949	1.36	(1.26–1.46)	1.01	926	1.27	(1.18–1.38)	0.96	894	1.03	(.95–1.11)	0.77
23F	PCV13	978	1.43	(1.34–1.53)	972	7.36	(6.71–8.08)	5.13	950	3.79	(3.49–4.13)	2.62	930	2.83	(2.61–3.07)	1.94
	Placebo	973	1.49	(1.40–1.60)	964	1.48	(1.38–1.59)	0.99	941	1.37	(1.27–1.47)	0.91	917	1.17	(1.08–1.26)	0.77

Immunoglobulin G values below the lower limit of quantitation (LLOQ) were set to 0.5 × lower limit of detection for purposes of summary and analysis. LLOQs are as follows: serotype 1, 0.02; serotype 3, 0.03; serotype 4, 0.02; serotype 5, 0.03; serotype 6A, 0.03; serotype 6B, 0.03; serotype 7F, 0.04; serotype 9V, 0.02; serotype 14, 0.04; serotype 18C, 0.02; serotype 19A, 0.02; serotype 19F, 0.03; serotype 23F, 0.03.

Abbreviations: CI, confidence interval; GMFR, geometric mean fold rise; GMT, geometric mean titer; PCV13, 13-valent pneumococcal conjugate vaccine.

[a]No. indicates number of subjects with valid and determinate assay results for the specified serotype at the given visit.

[b]GMCs were calculated using all subjects with available data for the specified blood draw.

[c]CIs are back-transformations of a CI based on the Student *t* distribution for the mean logarithm of the concentrations.

[d]GMFRs were calculated using all subjects with available data from both the before-vaccination and after-vaccination blood draws.

IgG GMCs showed a similar pattern with lower GMCs for all serotypes in PCV13 recipients ≥80 years of age at vaccination compared to younger age groups, but remained above baseline and the corresponding GMCs in the placebo group at each postvaccination time point (Supplementary Table 4). Lower GMCs in PCV13 recipients ≥80 years of age at vaccination were especially seen in serotypes 1, 3, 6A, 6B, 18C, 19A, 19F, and 23F. There were no differences in fold increase (Supplementary Table 4) or the proportion of subjects reaching a ≥4-fold increase in IgG concentration with a minimal level of 1.00 μg/mL between the different age groups (Supplementary Table 5).

Impact of Comorbidity

OPA GMTs in PCV13 recipients with 1 or more self-reported underlying medical conditions remained above baseline values at all postvaccination time points for each PCV13 serotype (Supplementary Table 6). Due to low numbers, effects of liver disease (n = 9 [0.5%]) and splenectomy (n = 2 [0.1%]) were not determined.

Overall, OPA and IgG responses as well as the proportion of subjects achieving a 4-fold increase in OPA or IgG levels following PCV13 were similar for subjects without any self-reported comorbidities and those with 1 or more underlying conditions (Supplementary Figure 2; Supplementary Tables 6–9).

DISCUSSION

A single dose of PCV13 in immunocompetent community-dwelling adults aged ≥65 years naive to pneumococcal vaccines elicited OPA GMTs and IgG GMCs that were significantly higher than baseline and the corresponding values in the placebo group at each postvaccination time point for 2 years after vaccination. In the eldest subjects (≥80 years at vaccination), postvaccination antibody levels remained well above baseline but were lower compared with younger age groups. Moreover,

Table 4. Pneumococcal Opsonophagocytic Activity Geometric Mean Antibody Titers per Serotype and Age Group in 13-Valent Pneumococcal Conjugate Vaccine Recipients

		Baseline			1 Month				12 Months				24 Months			
Serotype	Age Group	No.[a]	GMT[b]	(95% CI[c])	No.[a]	GMT[b]	(95% CI[c])	GMFR[d]	No.[a]	GMT[b]	(95% CI[c])	GMFR[d]	No.[a]	GMT[b]	(95% CI[c])	GFMR[d]
1	65–69 y	393	10	(9.7–10.6)	388	107	(90.9–126.0)	11	377	32	(27.7–37.1)	3	371	24	(20.9–27.4)	2
	70–79 y	471	10	(9.7–10.6)	469	98	(84.6–112.4)	10	455	33	(29.2–37.1)	3	446	21	(19.1–23.4)	2
	≥80 y	111	10	(9.1–10.9)	108	67	(48.4–93.7)	7	109	27	(20.3–35.2)	3	107	21	(16.3–26.4)	2
3	65–69 y	389	8	(7.7–9.2)	382	60	(52.2–69.2)	7	373	18	(16.0–20.9)	2	367	14	(12.1–15.4)	2
	70–79 y	466	8	(7.1–8.1)	461	58	(51.2–66.6)	8	449	19	(17.2–21.7)	3	440	12	(11.2–13.7)	2
	≥80 y	111	8	(6.6–8.9)	105	59	(43.4–79.3)	8	106	20	(15.2–25.3)	3	108	13	(10.6–16.3)	2
4	65–69 y	380	22	(19.0–26.5)	385	1580	(1350.3–1848.4)	69	366	360	(294.7–439.7)	15	363	183	(147.8–227.3)	8
	70–79 y	458	19	(16.9–22.2)	464	1280	(1090.0–1504.3)	67	449	295	(244.9–354.5)	15	439	173	(142.7–209.7)	9
	≥80 y	108	17	(13.2–21.6)	104	969	(639.9–1467.1)	56	105	216	(141.6–328.8)	12	102	127	(82.0–197.4)	7
5	65–69 y	390	15	(14.9–15.9)	377	104	(88.0–122.6)	7	376	42	(36.8–48.1)	3	370	36	(31.7–40.5)	2
	70–79 y	467	16	(15.2–16.3)	455	109	(93.5–126.5)	7	455	47	(41.5–53.6)	3	443	39	(34.9–44.3)	2
	≥80 y	110	15	(14.4–15.6)	106	88	(65.6–119.3)	6	107	40	(31.0–50.5)	3	105	33	(26.1–41.5)	2
6A	65–69 y	368	70	(59.3–83.3)	390	2072	(1763.1–2434.0)	28	369	767	(652.3–901.6)	10	356	417	(353.7–492.5)	6
	70–79 y	437	62	(53.1–71.9)	467	1752	(1503.5–2042.7)	28	446	700	(600.4–815.8)	11	424	386	(328.8–454.2)	6
	≥80 y	105	51	(38.4–68.3)	106	1016	(719.2–1436.6)	20	106	443	(306.7–641.1)	9	101	265	(188.7–373.5)	6
6B	65–69 y	357	107	(87.5–130.3)	380	2187	(1850.8–2583.1)	19	363	841	(709.6–997.8)	7	350	547	(457.5–655.2)	5
	70–79 y	426	96	(80.6–114.8)	461	1747	(1491.0–2047.8)	17	443	603	(510.0–712.6)	6	432	395	(332.7–470.1)	4
	≥80 y	102	82	(57.1–118.3)	102	1080	(722.6–1614.4)	14	106	428	(284.4–643.0)	6	105	290	(195.9–429.3)	4
7F	65–69 y	376	176	(159.5–194.7)	389	2001	(1773.3–2257.8)	11	377	700	(624.4–784.7)	4	366	439	(392.9–490.6)	2
	70–79 y	452	162	(149.4–175.3)	469	1671	(1488.9–1876.2)	10	454	679	(606.8–759.6)	4	445	407	(366.9–452.5)	2
	≥80 y	108	151	(126.7–179.6)	105	1325	(982.6–1787.3)	9	108	542	(420.3–697.8)	4	105	374	(296.0–471.4)	2
9V	65–69 y	384	251	(230.8–273.2)	379	1237	(1070.9–1429.8)	5	370	560	(495.7–632.6)	2	359	403	(359.2. 452.4)	2
	70–79 y	461	233	(217.9–248.9)	460	1047	(925.4–1185.5)	4	450	540	(486.7–599.7)	2	435	361	(329.5–394.9)	2
	≥80 y	107	229	(199.3–263.1)	105	815	(625.6–1060.8)	4	105	444	(352.6–558.7)	2	103	307	(254.4–370.0)	1
14	65–69 y	383	150	(123.5–183.1)	383	1088	(927.1–1277.7)	7	372	585	(501.9–681.9)	4	365	432	(366.8–508.1)	3
	70–79 y	461	122	(103.2–143.8)	461	976	(852.8–1117.1)	8	454	544	(475.9–620.9)	4	444	399	(344.8–462.1)	3
	≥80 y	108	75	(54.1–105.2)	105	730	(522.0–1022.0)	11	106	378	(269.3–530.9)	5	106	253	(182.5–349.9)	4
18C	65–69 y	387	46	(39.3–53.7)	388	1659	(1389.7–1981.4)	37	374	477	(397.8–573.1)	11	366	342	(284.5–411.5)	8
	70–79 y	468	45	(38.8–51.5)	468	1427	(1207.0–1687.6)	32	449	434	(365.4–516.0)	9	444	299	(250.8–355.9)	7
	≥80 y	108	40	(29.8–52.7)	106	1158	(769.1–1744.1)	28	107	337	(227.2–500.2)	8	106	201	(136.9–295.5)	5
19A	65–69 y	392	32	(27.7–36.7)	389	827	(711.5–960.4)	26	375	246	(212.4–285.7)	8	369	188	(161.6–218.3)	6
	70–79 y	467	30	(26.3–33.7)	470	638	(549.9–740.0)	21	456	225	(195.5–258.7)	7	443	150	(129.8–173.5)	5
	≥80 y	110	28	(20.9–37.4)	107	592	(420.6–833.9)	22	109	191	(136.6–267.0)	7	106	138	(97.6–194.8)	5
19F	65–69 y	386	38	(34.4–41.7)	373	644	(539.7–768.0)	17	363	186	(157.2–220.3)	5	360	133	(113.2–156.3)	3
	70–79 y	464	38	(34.7–42.0)	455	567	(476.6–673.5)	15	452	187	(160.5–217.8)	5	437	127	(109.5–146.8)	3
	≥80 y	108	36	(29.6–43.5)	101	424	(285.8–629.0)	12	107	154	(109.2–217.3)	5	105	116	(83.5–161.1)	3
23F	65–69 y	384	15	(13.1–18.0)	383	420	(334.7–525.9)	26	366	121	(96.3–151.9)	8	364	84	(67.0–105.3)	5
	70–79 y	463	12	(10.9–14.3)	461	286	(230.6–355.2)	23	451	98	(79.5–119.6)	7	440	65	(53.5–79.2)	5
	≥80 y	108	11	(8.7–14.3)	105	204	(128.4–324.0)	18	107	81	(53.4–122.2.)	7	106	50	(33.8–74.9)	4

Opsonophagocytic activity values below the lower limit of quantitation (LLOQ) were set to 0.5 × LLOQ for purposes of summary and analysis. LLOQs are as follows: serotype 1, 18; serotype 3, 12; serotype 4, 21; serotype 5, 29; serotype 6A, 37; serotype 6B, 43; serotype 7F, 210; serotype 9V, 345; serotype 14, 35; serotype 18C, 31; serotype 19A, 18; serotype 19F, 48; serotype 23F, 13.

Abbreviations: CI, confidence interval; GMFR, geometric mean fold rise; GMT, geometric mean titer.

[a]No. indicates number of subjects with valid and determinate assay results for the specified serotype at the given visit.

[b]GMTs were calculated using all subjects with available data for the specified blood draw.

[c]CIs are back-transformations of a CI based on the Student *t* distribution for the mean logarithm of the titers.

[d]GMFRs were calculated using all subjects with available data from both the before-vaccination and after-vaccination blood draws.

there was no apparent difference in immune responses to PCV13 between those with self-reported comorbidities and healthy older adults. However, this study was not powered to assess statistical differences among age and comorbidity subgroups.

To our knowledge, we are the first to report on the immunogenicity of PCV13 in a large placebo-controlled cohort of older adults in different age and comorbidity groups. Our findings are in line with results from smaller studies on the immunogenicity of PCV13 in older adults [11, 12, 16] and extend these observations

up to 24 months postvaccination in immunocompetent, community-dwelling adults naive to pneumococcal vaccinations. A large recent study by Frenck et al in adults aged 50–59 years reports that immune responses elicited by PCV13 sustain up to 5 years postvaccination [14]. We, however, also confirm that in older age groups, immune responses are generally lower than in younger age groups [29–32], though this was not corrected for the presence of comorbidities. Moreover, with respect to comorbidities, our data confirm that there are no apparent differences between healthy older adults and those with common comorbidities (excluding immunocompromising comorbidities) [33].

Although there is no consensus for a clinically meaningful empirically predefined level of protection in adults, clinical data support functional antibody and OPA as the basis for protection [34]. Based upon the observed immunogenicity, it would be expected that the efficacy of PCV13 in older adults is not greatly influenced by increasing age or common comorbidities. Within CAPiTA, the efficacy of PCV13 appears to decrease with increasing age, but the study was not powered to demonstrate efficacy by age group [18]. The clinical impact of lower immune responses in adults ≥80 years of age at vaccination may also be confounded by other age-related factors and comorbidities.

In children, an IgG concentration of 0.35 μg/mL after the primary series of PCV is regarded as a correlate of protection against IPD [35]. However, as vaccine effectiveness differs per serotype, so does the expected serological level of protection [36]. In our study in older adults, IgG responses to serotype 3 are somewhat lower than responses to other serotypes. Effectiveness of PCV13 against serotype 3 IPD differs with recent studies reporting 79.5% in US children [37] and 68% and 44% in UK children and adults [9], respectively. Nonetheless, vaccination with PCV13 in CAPiTA resulted in apparent clinical protection against serotype 3 CAP in older adults (PCV13 recipients: 7 CAP episodes by serotype 3; placebo group: 16 CAP episodes by serotype 3) [38]. However, CAPiTA was not powered to evaluate serotype-specific efficacy of PCV13.

PCVs elicit T cell-dependent immunological memory with the potential for recall response to natural exposure or revaccination. It remains unclear if PCVs indeed prolong the period of protection against VT pneumococcal disease compared to PPVs, especially in older adults in whom the ability to establish new memory responses is reduced due to a progressive loss of naive cells [16, 36]. Nonetheless, vaccine efficacy within CAPiTA was sustained throughout the trial duration (approximately 4-year mean follow-up) without evidence of waning efficacy [37]. Moreover, revaccination of adults 50–65 years of age with PCV13 after 4 years shows no hyporesponsiveness and induces greater OPA GMTs for half of the serotypes as compared to the first vaccination with PCV13 [9]. In healthy adults, circulating memory B-cell numbers 2 years postvaccination with PCV7 were better predicted by serotype-specific IgG concentrations before vaccination than by early postvaccination antibody responses [38]. For this reason, long-term immunogenicity data are needed to evaluate the mechanism and period of protection of a single dose of PCV13 in older adults and may depend more on biological age than chronological age [16].

Caution is needed when interpreting the results of this study. First of all, the reported results on the effect of age and comorbidities are exploratory, as the study was not powered to assess any statistical differences between different age and comorbidity groups or individual serotypes. Furthermore, comorbidities were self-reported and only assessed at baseline.

CONCLUSIONS

A single dose of PCV13 elicits high titers of functional OPA and IgG antibodies during the first 2 years postvaccination in community-dwelling immunocompetent older adults aged ≥65 years naive to pneumococcal vaccines. Within the limitations of the study, adults aged ≥80 years at vaccination generally exhibited lower postvaccination antipneumococcal responses, but levels remained above baseline. There was no apparent difference in immune responses to PCV13 between those with self-reported comorbidities and healthy older adults. Long-term immunogenicity data are needed to evaluate the period of protection of a single dose of PCV13 in older adults.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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