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Immunogenicity and safety of the 13-valent pneumococcal conjugate vaccine compared to the 23-valent pneumococcal polysaccharide vaccine in elderly Japanese adults

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Abbreviations: AE, adverse event; CAP, community-acquired pneumonia; CAPiTA, Community-Acquired Pneumonia Immunization Trial in Adults; CRM_{197}, cross-reactive material 197; GMFR, geometric mean fold rise; GMT, geometric mean titer; IPD, invasive pneumococcal disease; LLOQ, lower limit of quantitation; OPA, opsonophagocytic activity; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine

Streptococcus pneumoniae is a major cause of severe disease worldwide, particularly in the elderly population. Due to increasing life expectancy in Japan and elsewhere, an effective vaccine which offers the possibility of prolonged protection is required. Protein conjugated pneumococcal vaccines, which have the ability to boost immunity (immunologic memory) on natural exposure or revaccination, may meet these requirements. An unconjugated 23-valent pneumococcal polysaccharide vaccine (PPSV23) has been available for decades; however data on protection against pneumonia are inconsistent. For the first time, a randomized, modified double-blind trial comparing the 13-valent pneumococcal conjugate vaccine (PCV13) with PPSV23 was conducted in PPSV23-naive adults ≥65 years of age in Japan. This study showed that statistically significantly greater functional antibody responses as measured by opsonophagocytic assays 1 month after vaccination were elicited in the PCV13 group (n = 366) compared with the PPSV23 group (n = 367) for 9 of the 12 serotypes in common with both vaccines and for serotype 6A, unique to PCV13. Local reactions collected within 14 days of vaccination were more frequent in the PCV13 (57.5%, 211/367) than PPSV23 (44.9%, 166/370) group, although severity was generally mild to moderate; systemic and adverse events were similar across groups. There were no treatment-related serious adverse events. Consistent with global studies comparing PCV13 with PPSV23, PCV13 use in Japanese subjects was safe and well-tolerated and elicited greater functional immune responses than PPSV23 for the majority of PCV13-serotypes. PCV13 has the potential to protect against pneumococcal disease in Japanese elderly adults.

Introduction

Disease caused by *Streptococcus pneumoniae* is a major cause of mortality worldwide, with incidence highest among the elderly.[1] In Japan, *S pneumoniae* is the most common etiologic agent of community-acquired pneumonia (CAP), associated with 24%–39% of all cases.[2-4] In 2012, pneumonia was the third leading cause of death among the Japanese elderly ≥65 years of age (98.8 cases per 100,000).[5] Adult invasive pneumococcal disease (IPD) surveillance was initiated in Japan in 2013.[6] From April 2013 to March 2014, the incidence rate of IPD in Japanese adults aged ≥65 years was 2.43/100,000 person-years, with a mortality rate due to IPD of 10.39%. The serotypes reported over this period in order of frequency included serotypes 3

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(18.6%), 19A (10.8%), 22F (9.8%), 6C, 15A, 6B, 14, 23A, 19F, 11A/E, 35B, 10A, 15B, 23F, 33F, 24F, 38, 9V, 6A, 7F, 12F, 15C, and 34.[6] In addition, increasing numbers of antibiotic-resistant strains of *S pneumoniae* in Japan[7] emphasize the importance of vaccination as a preventive strategy.

Two pneumococcal vaccines are currently available for adults in Japan: a 23-valent pneumococcal polysaccharide vaccine (PPSV23), which is a part of the national immunization program (NIP), and a 13-valent pneumococcal conjugate vaccine (PCV13), which is available on the private market.[8] PCV13 coverage against IPD in 2013 was estimated at 48.0% for adults; PPSV23 coverage was estimated at 69.6%.[6] Protein conjugated vaccines such as PCV13 are thought to have immunologic advantages over free polysaccharide pneumococcal vaccines.[9] By conjugating the capsular polysaccharide to a carrier protein (CRM_{197}), PCV13 elicits memory B cells indicating a T cell–dependent response.[9,10] Immunologic memory on subsequent natural exposure or revaccination may sustain PCV13 protective antibody responses.

The aim of the current study was to compare the immunogenicity and safety of PCV13 to PPSV23 in Japanese adults aged ≥65 years who were naive to pneumococcal vaccines. This study was conducted to support licensing of PCV13 for adults in Japan.

Materials and Methods

Study design

This was a phase 3, randomized, modified double-blind, multicenter study conducted at 8 sites in Japan between 22 June 2012 and 25 Oct 2012. The primary objective for the 12 serotypes common to both PCV13 and PPSV23 was to demonstrate noninferiority of the immune responses elicited by PCV13 compared with PPSV23; and to demonstrate that PCV13 elicits a statistically significantly higher immune response than PPSV23 for serotype 6A, a serotype unique to PCV13. The secondary objective was to demonstrate that the immune responses induced by PCV13 were statistically significantly higher than the immune responses induced by PPSV23 for at least some of the 12 common serotypes and serotype 6A. The safety objective was to assess the safety profile of PCV13. This study was undertaken in accordance with the Declaration of Helsinki and International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice. The protocol was approved by the following institutional review boards: the Kyushu Clinical Pharmacology Research Clinic IRB, Fukuoka; the Yokohama Minoru Clinic IRB, Kanagawa; and the Sone Clinic IRB, Tokyo.

Subjects

The study population included healthy Japanese men and women ≥65 years of age who provided informed consent and would be available for the duration of the study. Adults with underlying chronic conditions that were stable for ≥12 weeks prior to vaccination were included. Subjects were ineligible if they were immunocompromised, had severe acute/chronic medical or psychiatric conditions, had a history of severe vaccine associated adverse reactions, had *S. pneumoniae* infection within the last 5 years, were vaccinated with a diphtheria-containing vaccine or toxoid within 6 months, received a blood product within the last 3 months, or had previously received a pneumococcal vaccination.

Vaccines and administration

PCV13 (Wyeth Vaccines; Lot Number 7-5095-012A and F93996) contains pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F (containing 2.2 μg of each saccharide, except for 4.4 μg of serotype 6B) individually conjugated to a nontoxic form of diphtheria toxin cross-reactive material 197 (CRM_{197}), 0.85% sodium chloride, 0.02% polysorbate 80, and 0.125 mg aluminum as aluminum phosphate. The vaccine is supplied in single-dose syringes without preservatives and stored at 2°C–8°C.

PPSV23 (Pneumovax 23®, Merck & Company, Inc.; Lot Number 9MN11R) consists of a purified capsular polysaccharide from 12 of the serotypes included in PCV13 (all except 6A), as well as 11 additional serotypes (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F). The vaccine contains 25 μg of each of the 23 purified polysaccharide serotypes per 0.5 mL dose of vaccine and contains phenol as a preservative. The vaccine was stored at 2°C–8°C.

Vaccines were administered by intramuscular injection in the deltoid muscle. Any licensed vaccine other than pneumococcal vaccine was permitted during the study but were not to be administered concurrently with the study vaccine.

Randomization

Eligible subjects were randomized in a 1:1 ratio to receive a single 0.5 mL dose of PCV13 or PPSV23. In the modified double-blind design, the vaccines were dispensed and administered by unblinded study staff members not involved in subsequent assessments. All other study staff members and subjects were blinded to the vaccine administered.

Immunogenicity assessments

OPA titers for the 13 serotypes in PCV13 were measured using serotype-specific microcolony OPA assays as described previously[11] in blood samples obtained immediately before and 1 month (28−42 days) after vaccination. Briefly, heat-inactivated sera were serially diluted 2.5-fold in assay plates in which target bacteria were added and incubated for 30 minutes at either 25°C or 37°C, depending on serotype, on a shaker. Baby rabbit serum (Pel-Freez, USA) and differentiated HL-60 cells (Catalog no. CCL240, ATCC, USA) were added and assay plates were incubated for 45 minutes at 37°C on a shaker. Surviving bacteria were measured by microcolony growth on filter plates and enumeration of microcolonies with a Cellular Technology Limited (CTL) ImmunoSpot Analyzer®. The OPA antibody titer was interpolated from the reciprocal of the 2 serum dilutions encompassing the point of 50% reduction in the number of bacterial colonies when compared to the control wells that did not contain immune serum. The OPAs were fully validated and both

acceptable precision (%RSD < 60%) and acceptable relative accuracy (bias between 67−150%) were demonstrated. OPA assays were performed in a central laboratory by the sponsor.

Safety assessments

Subjects recorded local reactions (redness, swelling, pain, limitation of arm movement) and systemic events (temperature, chills, fatigue, headache, vomiting, rash, decreased appetite, new or aggravated muscle or joint pain,) in an electronic diary in the evening for 14 days after vaccination. The largest diameter of any redness or swelling was measured using a caliper. Axillary temperature was measured using a digital thermometer and fever was defined as a temperature of ≥37.5°C. The highest daily temperature was recorded.

The investigator collected other adverse events (AEs) which were not prompted by the e-diary for 29–43 days after vaccination using the case report form. Assessments were based on clinical evaluation as well as responses to nonspecific questions.

Statistical Methods

Sample size estimation

A sample size of approximately 330 evaluable subjects per vaccine group was to provide at least 90% power to demonstrate noninferiority of PCV13 versus PPSV23 for 12 common serotypes and statistical significance of PCV13 relative to PPSV23 for serotype 6A. Data from previous trials were used for computations.[12–14] Assuming a dropout rate of approximately 10%, 367 subjects per group were to be enrolled.

Table 1. Comparisons of pneumococcal OPA GMTs for the 12 common serotypes and serotype 6A 1 month after vaccination

	Vaccine Group			
	PCV13	PPSV23	Comparison	
Serotype	GMT[a], N=350–366	GMT[a], N=349–367	Ratio[b]	(95% CI[c])
1	103	78	1.3	(0.99, 1.75)
3	44	61	0.7	(0.59, 0.89)
4	1016	392	2.6	(1.96, 3.44)
5	347	118	2.9	(2.22, 3.86)
6A	2122	676	3.1	(2.38, 4.14)
6B	1995	1440	1.4	(1.10, 1.75)
7F	1901	1361	1.4	(1.12, 1.74)
9V	858	379	2.3	(1.59, 3.24)
14	1028	1059	1.0	(0.77, 1.23)
18C	2015	938	2.1	(1.61, 2.86)
19A	985	429	2.3	(1.81, 2.92)
19F	773	388	2.0	(1.42, 2.79)
23F	456	180	2.5	(1.84, 3.49)

[a]Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.
[b]Ratio of GMTs (PCV13 / PPSV23) is calculated by back transforming the mean difference between vaccine on the logarithmic scale.
[c]CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (PCV13–PPSV23).

Analysis populations

The primary analysis population was the evaluable immunogenicity population, which included eligible subjects who received the study vaccine to which they were randomly assigned and had at least one valid and determinate assay result, had pre- and post-vaccination blood samples taken within the prescribed time window and had no major protocol violations. The all-available immunogenicity population included all subjects who had ≥1 valid and determinate assay result (data were similar and not presented here). The safety population included all vaccinated subjects.

Immunogenicity analysis

For the PCV13 serotypes, titers below the lower limit of quantitation (LLOQ) were set to a value of 4 (half of the limit of detection, which is the same for all assays). Serotype-specific OPA titers were logarithmically transformed for analysis. OPA geometric mean titers (GMTs) were computed for each serotype. Corresponding 95% CIs were constructed by back transformation of the CIs based on the Student *t* distribution for the mean of the logarithmically transformed assay results. To assess differences between vaccines, 2-sided 95% CIs for the ratios of GMTs were constructed by back transformation of the CIs for the mean difference of the logarithmically transformed assay results computed using the Student *t* distribution. Noninferiority was demonstrated if the lower limit of the 2-sided, 95% CI for the ratio of OPA GMT (PCV13 relative to PPSV23) for the 12 common pneumococcal serotype comparisons was >0.5. Statistical significance was demonstrated if the lower limit of the 2-sided, 95% CI for the ratio of GMTs was >1 for the 12 common serotypes or >2 for serotype 6A, a serotype unique in PCV13. In addition, for serotype 6A, the difference in proportions of subjects achieving a 4-fold rise in OPA titer (PCV13–PPSV23) was calculated; statistical significance was demonstrated if the lower limit of the 2-sided, 95% CI was >0. A 4-fold increase in antibody titers postvaccination is a generally accepted method for demonstrating immune responses to vaccines where an antibody titer threshold of protection has not been defined.[15-17]

Safety analysis

For safety assessments, the proportion of subjects with local reactions, systemic events, and AEs were determined; for differences of the proportion of subjects with local reactions and systemic events between vaccine groups *p*-values were generated based on Chan and Zhang.[18] AEs were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA). The statistical software system used for generation of the tables and figures was SAS® 9.2 Release (SAS Institute, Cary, NC).

Results

Disposition of subjects and baseline characteristics

A total of 764 Japanese adults were randomized to receive PCV13 (n = 382) or PPSV23 (n = 382); only one PCV13 recipient discontinued for "family matters." Demographic

characteristics were similar between vaccine groups. Overall, 50.4% (385/764) of subjects were female. Mean age was 69.9 ± 3.9 years; all subjects were Japanese.

During an initial trial period to test the study procedures, the sponsor became aware that the treatment assignment could potentially be unblinded by sponsor employees conducting the study, although actual unblinding did not occur. Unblinding could potentially be achieved by inappropriate access to information in the electronic drug distribution system or on the study vaccine receipt form when combined with information on the case report form. The study vaccines and related forms and systems were newly prepared and access was limited to assure the maintenance of the study blind before any further subjects were enrolled. The first 30 subjects enrolled were excluded from the evaluable immunogenicity population; these 30 subjects were replaced, leading to a higher number of overall subjects in the study relative to the initial sample size calculation. The evaluable immunogenicity population consisted of 733 subjects (PCV13, n = 366; PPSV23, n = 367).

Of note, after this study and analyses were completed, possible irregularities at one of the 8 sites in Japan were identified in a prior study by another sponsor. Based on further assessment of the conduct of the current study at this site, Pfizer decided to exclude immunogenicity and safety analyses of this site (n = 100; PCV13 = 49, PPSV23 = 51) for marketing authorization in Japan. However, post hoc analyses did not reveal any differences in the statistical inferences drawn from the comparisons between the 2 vaccine groups when analyzed with and without this site. Therefore, for completeness, the data presented herein include the safety and immunogenicity data from this site.

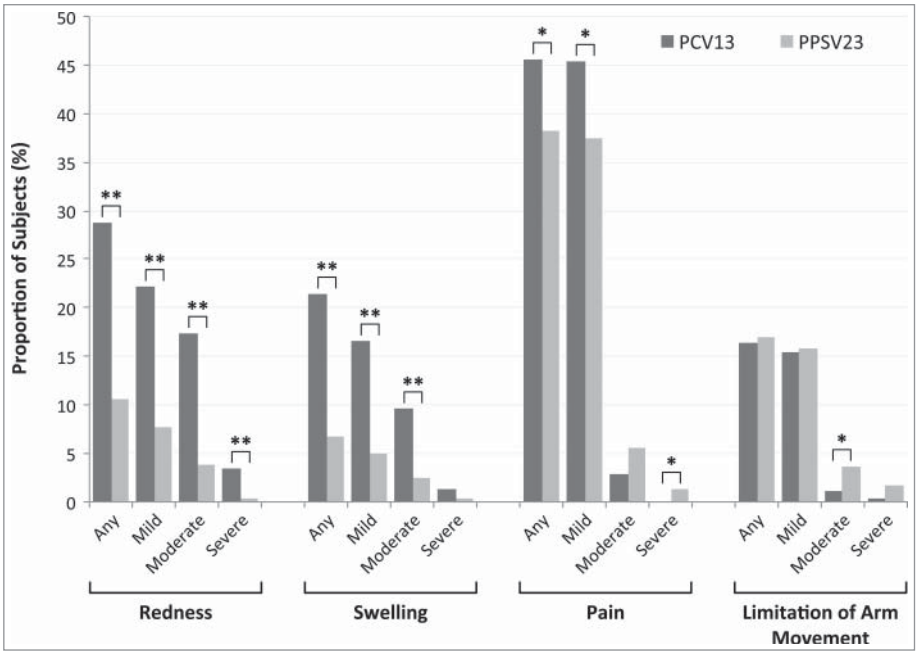

Figure 1. Subjects reporting local reactions within 14 days after vaccination. *P-value < 0.05, **P-value ≤ 0.01; based on Chan & Zhang for the difference in proportion of subjects (PCV13–PPSV23). Redness and swelling: mild = 2.5–5.0 cm, moderate = 5.1–10.0 cm, severe is >10.0 cm. Pain: mild = awareness, but easily tolerated; moderate=discomfort causing interference with usual activity; severe = incapacitating. Limitation of arm movement: mild=some limitation; moderate=unable to move above head but able to move above shoulder; severe = unable to move above shoulder. PCV13 = 13-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine.

Immunogenicity

Serotype-specific OPA GMTs at baseline were similar in the 2 vaccine groups (PCV13 OPA GMT range 5–109; PPSV23 OPA GMT range 5–155). OPA GMTs 1 month post-vaccination increased significantly in both vaccine groups with geometric mean fold rise (GMFR) ranging from 9.0 to 116.1 in the PCV13 group and 8.2 to 65.4 in the PPSV23 group. GMFRs were numerically higher in the PCV13 group compared with the PPSV23 group for all serotypes except serotype 3 (**Table S1**). One month after vaccination, PCV13 OPA GMTs were noninferior to PPSV23 for all 12 common serotypes and statistically significantly higher in the PCV13 group for 9 (serotypes 4, 5, 6B, 7F, 9V, 18C, 19A, 19F, 23F) of the 12 common serotypes and serotype 6A (**Table 1**). The proportions of subjects achieving a 4-fold increase in OPA titer for serotype 6A (a serotype unique to PCV13) one month after vaccination were statistically significantly higher in the PCV13 (74.0%) group compared with the PPSV23 (47.2%) group, with a difference of 26.8% (95% CI: 19.3%, 34.0%). With the exception of serotypes 3 and 14, reverse cumulative distribution curves (RCDC) for each of the serotypes showed that OPA GMTs were higher across the full range of antibody titers for PCV13 compared with PPSV23 (**Fig. 2**). For serotype 3, the curve was generally higher for PPSV23 compared with PCV13; for serotype 14 the curve was similar for both vaccines. Although there is no threshold of protection defined for pneumococcal serotypes in adults, a high proportion of subjects achieved the serotype specific OPA functional antibody thresholds (as defined by the lower limit of quantitation; LLOQ, **Fig. 2**) for all serotypes including serotype 3 (serotype 3: 82.2% in PCV13 group and 86.1% in PPSV23 group).

Safety

Local reactions occurring within 14 days after vaccine administration were reported by 57.5% (211/367) of PCV13 recipients and 44.9% (166/370) of PPSV23 recipients (P<0.001). The percentages of subjects with any redness, swelling, or pain were statistically significantly higher in the PCV13 group than in the PPSV23 group (**Fig. 1**). The percentage of subjects who experienced any limitation of arm movement was similar

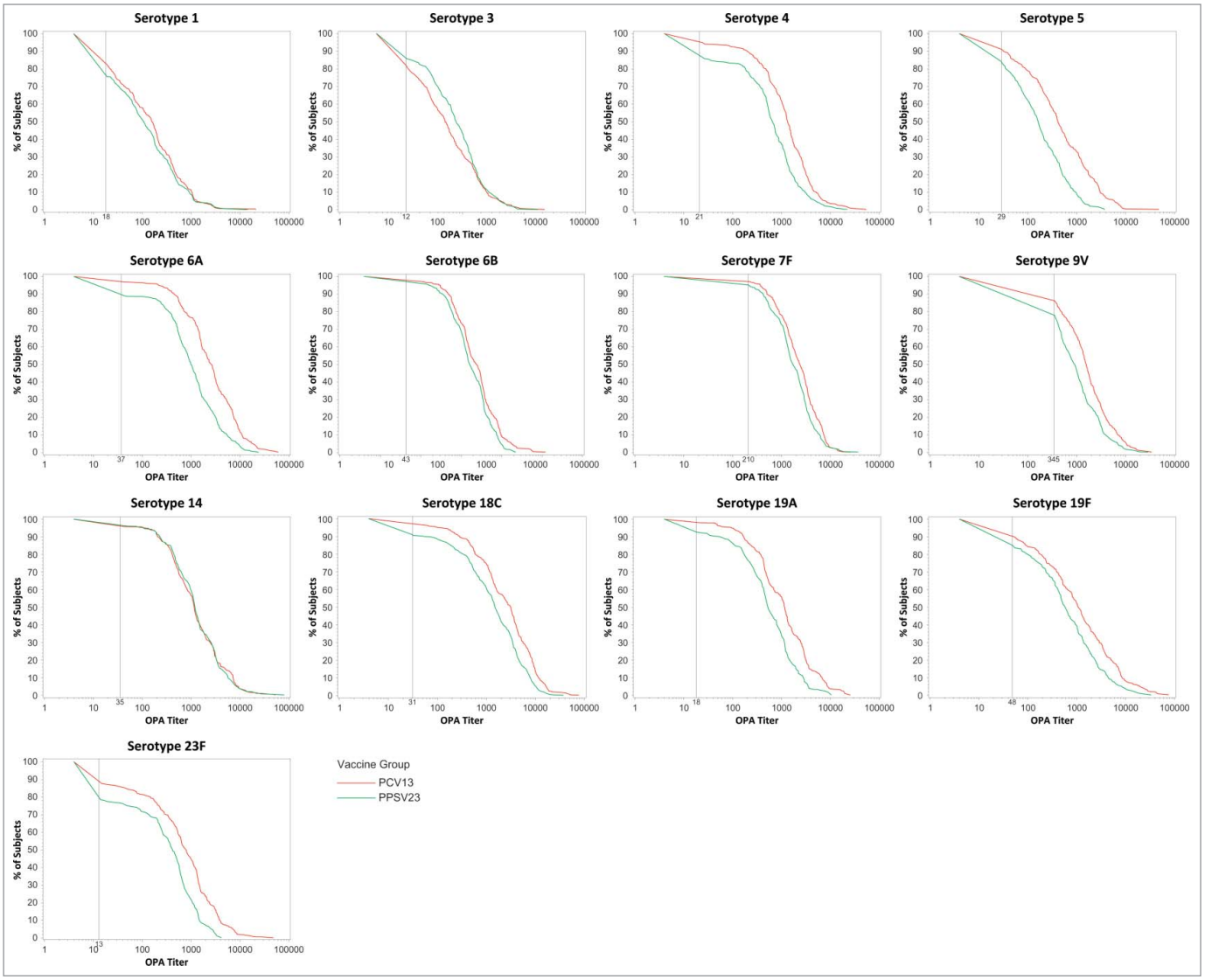

Figure 2. Reverse cumulative distribution curves for OPA antibody titers 1 month postvaccination. OPA = opsonophagocytic activity; PCV13 = 13-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine. The lower limit of quantitation (functional antibody titer thresholds) for each serotype is marked: serotype 1, 1:18; serotype 3, 1:12; serotype 4, 1:21; serotype 5, 1:29; serotype 6A, 1:37; serotype 6B, 1:43; serotype 7F, 1:210; serotype 9V, 1:345; serotype 14, 1:35; serotype 18C, 1:31; serotype 19A, 1:18; serotype 19F, 1:48; and serotype 23F, 1:13.

between groups (**Fig. 1**). In both groups, the majority of the local reactions were mild or moderate in intensity. The mean duration of redness was slightly longer for recipients of PCV13 (4.3 days) than PPSV23 (1.9 days). The mean durations of swelling, pain, and limitation of arm movement were similar in both vaccine groups and did not exceed 2.8 days.

The percentages of subjects who experienced systemic events were similar between vaccine groups with one exception; a significantly higher percentage of PCV13 recipients ($P = 0.004$) reported rash (**Table 2**). New muscle pain, fatigue, and headache were most frequently reported. Fever ≥37.5°C and fever ≥38.0°C was uncommon (≤3.6%) across vaccine groups. Subjects with fever of ≥39°C were confirmed by the investigator to be data entry errors (3 subjects in the PCV13 group and the 2 subjects in the PPSV23 group); these subjects were not included in the analysis. Across vaccine groups, the mean duration for fever ≥37.5°C did not exceed 1.7 days and for the other systemic events did not exceed 4.1 days. The percentages of subjects who experienced any AE were similar among PCV13 and PPSV23 recipients (6.8% vs 7.1%, respectively). During the study, one AE was assessed as serious (pancreatic carcinoma) in the PCV13 group; this was not considered vaccine related. Most of the AEs include diseases and conditions commonly observed among older adults.

Discussion

This is the first study in Japan comparing immunogenicity and safety of PCV13 and PPSV23 administered to

Table 2. Subjects reporting systemic events within 14 days after vaccination

Event	Vaccine Group		
	PCV13 n (%)N[a] = 345−352	PPSV23 n (%)N[a] = 357−362	Comparison *p*-Value[b]
Fever[c] ≥38°C	4 (1.2)	3 (0.8)	0.765
≥38°C but <38.5°C	4 (1.2)	2 (0.6)	0.519
≥38.5°C but <39°C	1 (0.3)	1(0.3)	>99
≥39°C but ≤40	0 (0.0)	0 (0.0)	>99
Fatigue	61 (17.3)	58 (16.0)	0.673
Headache	33 (9.4)	42 (11.6)	0.341
Chills	10 (2.9)	4 (1.1)	0.102
Rash	31 (8.9)	13 (3.6)	0.004
Vomiting	4 (1.1)	2 (0.6)	0.520
Decreased Appetite	13 (3.7)	18 (5.0)	0.456
New Muscle Pain	65 (18.4)	63 (17.4)	0.777
Aggravated Muscle Pain	14 (4.0)	14 (3.9)	0.998
New Joint Pain	27 (7.7)	25 (7.0)	0.741
Aggravated Joint Pain	10 (2.9)	11 (3.1)	0.933

[a]n = Number of subjects reporting the specified event.
[b]*P*-value (based on Chan & Zhang) for the difference in proportions, PCV13 – PPSV23.
[c]Temperatures ≥39°C were confirmed to be data entry errors and were excluded from the analyses.

pneumococcal vaccine naive adults aged ≥65 years. The current study addresses limitations of a prior study in Japan that did not include a comparison of PCV13 and PPSV23; results of this previous study showed that PCV13 elicited similar or somewhat higher immune responses in Japanese adults aged ≥65 years than those observed in the present study.[19] A limitation of the current study was that there were no clinical endpoints comparing the effectiveness of these 2 vaccines. However, the recently completed Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) 65 years of age and older in the Netherlands with approximately 85,000 subjects partially addressed this limitation by examining the clinical efficacy of PCV13 compared to placebo, demonstrating PCV13 is efficacious against vaccine-type CAP, including non-bacteremic CAP and vaccine-type IPD.[20-22]

In the current study, PPSV23 was chosen for comparison as it is currently licensed and part of the NIP in Japan for adults ≥65 years of age.[8] PPSV23, a free polysaccharide vaccine which elicits T cell−independent immune responses, has demonstrated efficacy against IPD, and in some settings, pneumonia;[23] however, the duration of protection of PPSV23 is limited to approximately 2–5 years.[24] The limited duration of protection of PPSV23 is associated with waning antibody concentrations and the T cell−independent nature of the PPSV23 immune responses, with little or no memory response on natural exposure; revaccination is required. Some studies have observed that immune responses of some PPSV23 serotypes are significantly reduced upon revaccination at a 6-month to 4-year interval, which raises the question of hyporesponsiveness.[25-29] Other studies in the United States[30,31] and in Japan[32] demonstrated that when subjects were revaccinated with PPSV23 after an interval longer than 5 years, the serotypes studied were immunogenic when compared with prevaccination levels. Antibody responses on revaccination, although lower, were generally sustained when compared with those after the initial vaccination. Based on these findings, it was concluded that significant hyporesponsiveness on revaccination was not observed when the time interval between vaccinations is extended.[26,28,30-32] However, it is still unclear if revaccination with PPSV23 at intervals longer than 5 years is adequate to maintain persistant antibody levels sufficient for extended protection against pneumococcal disease, as there is no threshold of protection defined for adults, and no efficacy studies to support this.

On the other hand, PCV13, a conjugated pneumococcal vaccine, elicits memory B cells indicating a T cell−dependent response.[9,10] This memory response may have the immunologic advantage of sustaining protective antibody responses upon subsequent natural exposure or revaccination. One US study showed that when PCV13 recipients received a second dose of PCV13 after approximately 4 years, immune responses were generally sustained compared to responses after the initial PCV13 vaccination, with many of the PCV13 serotypes showing statistically significantly higher responses.[27] Although the duration of protection provided by PCV13 is not known, the CAPiTA study recently demonstrated a reduction of vaccine-type CAP cases in PCV13 vaccinated individuals that lasted at least 4 years.[20,21] However, if protection from initial vaccination should wane, the US study on the impact of PCV13 on subsequent vaccination[27] clearly demonstrates the ability to revaccinate with PCV13 after an appropriate interval, thereby maintaining or increasing antibody levels; this may optimize protection. Surveillance data from many countries will continue to monitor IPD incidence to assess the need for revaccination.[6,33-36]

In the current study, functional antibody responses as measured by OPA were noninferior for all serotypes and statistically significantly higher for the majority of serotypes after PCV13 compared with PPSV23. For both serotypes 1 and 14, immune responses to PCV13 were similar to PPSV23; the reason why responses were not higher is unknown. Regardless, these

serotypes in PCV13 are expected to be as effective as PPSV23 in adults against pneumococcal disease.[37] Only serotype 3 elicited statistically significantly lower responses after PCV13 compared with PPSV23; the underlying immune mechanism and the clinical relevance is unknown. Nevertheless, serotype 3 elicited a 9-fold increase in immune response from baseline to 1 month after PCV13 vaccination. This increase in immune response, together with the ability of PCV13 to elicit a memory response, suggests that serotype 3 may have the potential to protect against pneumococcal disease. The CAPiTA study, as described above, demonstrated a reduction of vaccine-type CAP cases, including cases caused by serotype 3, in PCV13 vaccinated individuals when compared with placebo;[20,21] surveillance data will continue to be monitored for PCV13 effectiveness in adults.[6,33-36]

In addition, PCV13 elicited a statistically significantly higher response for serotype 6A, contained only in PCV13. Of note, the functional OPA antibody response against serotype 6A is cross-reactive with serotype 6C,[11] a serotype that was recently demonstrated to cause IPD.[6,38,39]

Of interest, prevaccination antibody titers were similar across vaccine groups, but fold rises were numerically higher after PCV13 compared with PPSV23 for all serotypes except serotype 3. Although a specific level of OPA antibody responses has not been shown to correlate with protection against pneumococcal disease in adults, OPA functional antibody responses are generally accepted as a correlate of vaccine-induced protection.[40] Furthermore, the reverse cumulative distribution curves showing proportion of responders for a given titer provide reassurance that, whatever the correlations of OPA responses and protection are, the proportion of responders after PCV13 administration is equivalent or higher than the proportion of responders after PPSV23.

Similar results were observed in studies in the United States and Europe conducted in PPSV23-naive adults 60 to 64 years of age and PPSV23 pre-immunized adults ≥65 years of age. In these studies, immune responses were noninferior for all serotypes and significantly higher for 8−10 of the 12 common serotypes and for serotype 6A after PCV13 compared with after PPSV23. For serotypes 3 and 14, the differences in responses between vaccines post vaccination were consistent with those observed in the current study.[12,13,27,41] As discussed above, a US study clearly demonstrated the ability to revaccinate PCV13 recipients with PCV13.[27] PCV13 was also shown to enhance responses to PPSV23.[12,27] This allows for PPSV23 to be given after PCV13 if broader serotype coverage is required. In the United States, for example, the Advisory Committee for Immunization Practices currently recommends that adults aged ≥65 years who are naive to pneumococcal vaccines receive a dose of PPSV23 by 6−12 months after PCV13 to cover the 11 additional serotypes not included in PCV13.[42] Given the similarity of the results in these studies with the current study, it is likely that studies examining the sequence of vaccine administration in Japanese adults would elicit similar responses. Finally, a study in subjects ≥80 years of age in Japan showed that PCV7 serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F elicited higher functional antibody responses in PCV7 compared with PPSV23 recipients; these differences were significantly higher for serotypes 4, 9V, 18C, and 23F.[43] It is particularly reassuring that elderly Japanese subjects ≥80 years of age are able to mount higher functional antibody responses after PCV7 compared with PPSV23, despite reports of immunosenescence in the elderly.[44]

As in other studies with PCV13,[12,19,45] in the current study, PCV13 was shown to have an acceptable safety and reactogenicity profile. Local reactions were mainly mild to moderate in severity and self-limiting, although they were statistically significantly higher among PCV13 recipients than PPSV23 recipients, possibly reflecting the higher immune responses observed after PCV13.[46] There were no related SAEs or deaths in this study.

In conclusion, taking into consideration the potential for the T cell–dependent immune response of PCV13 to establish immunologic memory (thereby enhancing subsequent responses to natural exposure), the generally higher immune responses for the PCV13 vaccine serotypes elicited by PCV13 compared with PPSV23, and the data from the CAPiTA study which support efficacy of PCV13,[20,21] this study supports the perspective that PCV13 has the potential for improved clinical efficacy against the substantial burden of IPD[6] and pneumonia[2] caused by PCV13-associated serotypes in Japan.

Disclosure of Potential Conflicts of Interest

CJ, YS, MY, BB, DC, WCG, DAS, BS-T, are all employees of Pfizer and may have stock or stock options. MS and RH disclose no conflicts of interest.

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Supplemental Material

Supplemental data for this article can be accessed on the publisher's website.

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