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Comparison of the immunogenicity and safety of polysaccharide and protein-conjugated pneumococcal vaccines among the elderly aged 80 years or older in Japan: An open-labeled randomized study

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ABSTRACT

An open-labeled randomized study was conducted to compare the immunogenicity and safety of polysaccharide (PPV23) or protein-conjugated pneumococcal vaccine (PCV7) among the elderly aged 80 years or older. A total of 105 nursing home residents were enrolled in this study. We analyzed the geometric mean concentration (GMC) of serotype-specific immunoglobulin G (IgG) and the geometric mean titer (GMT) of the opsonization index (OI) for serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. The GMCs of serotype-specific IgG and the GMTs of the OI significantly increased one month after vaccination in both groups for all seven serotypes evaluated. In the PCV7 group, study subjects with serotypes 4, 9V, 18C, and 23F exhibited statistically significant elevations in both serotype-specific IgGs and OIs compared to those of the PPV23 group. Both vaccines were tolerated without any severe adverse events, and no differences in systemic adverse events were observed between the two groups, although adverse reactions such as redness and localized swelling were more common in the PCV7 group. Our data demonstrated that the GMCs of serotype-specific IgG and the GMTs of the OI were higher in the PCV7 group compared to those in the PPV23 group. Our study also confirmed the safety of both the PCV7 and PPV23 vaccines in elderly people aged 80 years or older.

1. Introduction

Streptococcus pneumoniae infection is a major cause of mortality and morbidity worldwide among the elderly. The 23-valent pneumococcal polysaccharide vaccine (PPV23) is widely recommended for administration to those who are at a high risk of *S. pneumoniae* infection, such as elderly people and splenectomy patients [1]. However, owing to the purified free polysaccharides that comprise its surface capsule, PPV23 does not elicit T cell-dependent immune responses and is a poor inducer of immunologic memory. Furthermore, vaccine-induced antibody titers may achieve insufficient levels and decrease annually, particularly 5 years after vaccination [2].

The conjugation of the capsular polysaccharide to a diphtheria protein stimulates not only B-cell immune response but also T cell-dependent immune responses and enhanced memory response at the time of boosting [3]. Therefore, pneumococcal conjugate vaccines produce superior immune responses, particularly in infants. For this reason, the heptavalent pneumococcal conjugate vaccine (PCV7) was licensed in 2000 in the United States and in 2009 in Japan. PCV7 also produces better immune responses than PPV23 in groups at higher risk of developing invasive pneumococcal diseases

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and pneumococcal pneumonia, such as individuals with HIV [4] or chronic obstructive pulmonary disease [5].

In healthy elderly people 50–80 years old, Goldblatt et al. [6] reported that PCV7 produced superior immunogenicity compared with PPV23. In recent years, the increasing number of elderly people over 80 years old hospitalized for pneumococcal pneumonia has been reported [7]. While pneumococcal vaccination is strongly recommended for this population, no data are currently available for comparison of the immunogenicity and safety between PCV7 and PPV23 for this age group. Therefore, we performed this prospective study to clarify these unknown aspects.

2. Materials and methods

2.1. Study subjects

The present study was a randomized, open-label study designed to compare the immunogenicity and safety of PCV7 (Prevenar; Pfizer) with those of PPV23 (Pneumovax; MSD). Data were collected between April 2011 and December 2012 from participants who were 80 years or older and had never received pneumococcal vaccinations. None of the participants had any documented history of pneumococcal infection. They were selected from five different nursing homes around Tokyo and were randomly assigned to either the PPV23 group or the PCV7 group using the sealed envelope system with a 1:1 allocation ratio. A total of 105 participants were enrolled in this study, and all participants provided written informed consent.

In addition, subjects were excluded if they had a history of any streptococcal vaccination, a history of anaphylactic reaction to diphtheria toxin, or symptoms of fever on the day of vaccination.

We set the sample size on the basis of a study by Goldblatt et al. [6] on the comparison of immunogenicity between PCV7 and PPV23 among adults aged 50–80 years. They assigned 33–60 subjects to a subgroup of one arm and showed higher geometric mean concentrations (GMCs) of serotype-specific IgG response in several serotypes.

This study was reviewed and approved by the Research Ethics Committee of Keio University School of Medicine (2010-231-2) and by the Research Ethics Committee of Kitasato University Kitasato Institute Hospital (1108-02). This trial was registered with the UMIN Clinical Trials Registry (UMIN000006132).

2.2. Vaccines

The PCV7 used in this study is currently licensed only for pediatric use in Japan. PCV7 contains polysaccharides of pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, which are conjugated to the protein carrier CRM197, a nontoxic variant of the diphtheria toxin. Each serotype-specific polysaccharide is conjugated separately prior to formulation as a multivalent vaccine. The vaccine contains aluminum phosphate as an adjuvant.

PPV23 contains a mixture of purified capsular polysaccharides from 23 different serotypes of *S. pneumoniae*: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F. This vaccine is adjuvant-free.

Each participant received 0.5 mL of either PPV23 or PCV7 via subcutaneous injection. PPV23 and PCV7 were dispensed and administered by members who were not blinded and not involved in subsequent data analysis.

2.3. Samples

Blood samples (10 mL) were drawn from all the subjects on the day of vaccination and approximately one month after vaccination. Sera were separated by centrifugation (3500 rpm, 15 min, 4 °C) and stored at −80 °C.

2.4. Enzyme-linked immunosorbent assay (ELISA)

Anti-pneumococcal immunoglobulin G (IgG) antibodies were measured by World Health Organization (WHO)-approved ELISA, using standard reference serum (89-SF or 007sp) and C-polysaccharide and 22F polysaccharide absorption, as previously reported [8,9]. The levels of serotype-specific IgGs for seven serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) were determined in both vaccination groups according to the WHO protocol (a detailed version of the protocol is available at http://www.vaccine.uab.edu/ELISAProtocol(89SF).pdf). These serotypes are covered by PCV7.

2.5. Multiplexed opsonophagocytic killing assay

A multiplexed opsonophagocytic killing assay for seven serotypes, 4, 6B, 9V, 14, 18C, 19F, and 23F, based on antibiotic-resistant strain target bacteria, was performed at the Research Institute for Microbial Diseases, Osaka University, as previously described [10]. The quality control serum used in each assay was prepared from the pooled sera of adults vaccinated with PPV23 or PCV7. The opsonization index (OI) was defined as the serum dilution capable of killing 50% of the bacteria, which was determined by using opsotiter3 software according to the WHO protocol (a detailed version of this protocol is available at www.vaccine.uab.edu/UAB-MOPA.pdf) [11]. Laboratory analysis, ELISA, and a multiplexed opsonophagocytic killing assay were performed by members who were blinded to vaccine allocation.

2.6. Adverse reactions

All patients were observed daily by medical staff to monitor body temperature and any local or systemic reactions, starting from the day of vaccination to day 7. Injections were graded based on the occurrence of several possible adverse events as follows: grade I (the reaction was present but easily tolerated), grade II (the reaction interfered with normal activity), and grade III (the reaction was severe or incapacitating).

2.7. Statistical analysis

Average antibody concentrations and the increases from baseline were expressed as geometric means. Differences in the GMCs of serotype-specific IgG and the geometric mean titers (GMTs) of the OI were assessed by the Wilcoxon matched-pairs signed-ranks test. For multiple comparisons, we calculated Bonferroni-adjusted P values. The frequencies of adverse reactions were compared between vaccinations by the Fisher exact test. Differences with $P < 0.05$ were considered to be statistically significant. Data analysis was performed by members who were blinded to vaccine allocation.

3. Results

3.1. Participant characteristics

Overall, 623 eligible participants were reviewed in the 5 nursing homes (Fig. 1). One hundred and five participants were enrolled in this study after they provided written informed consent. Five subjects were subsequently dropped from the study prior to vaccination (2 subjects were hospitalized, 2 subjects left the nursing home, and 1 subject died). Consequently, 100 subjects were vaccinated (Table 1); of these, 49 received PPV23 and 51 received PCV7. The mean ages at enrollment were 88.3 years for the PPV23 group and 87.7 years for the PCV7 group, with 45 subjects in their

Table 1
Participants characteristics.

Characteristics	PPV23[a] ($n=49$)	PCV7[b] ($n=51$)	P value
Age, years	88.3 ± 1.4	87.7 ± 1.5	0.29
Male, %	12 (24.5)	11 (21.6)	
Female, %	37 (75.5)	40 (78.4)	
Height, cm	145.1 ± 3.9	146.5 ± 2.2	0.24
Weight, kg	45.9 ± 2.4	46.0 ± 2.1	0.47
Hypertension, %	34 (69.4)	32 (62.7)	
Diabetes mellitus, %	15 (30.6)	18 (35.2)	
Old cerebral infarction, %	17 (34.7)	14 (27.5)	
Dementia, %	15 (30.6)	13 (25.5)	
Dyslipidemia, %	14 (28.6)	12 (23.5)	
Neck of femur fracture, %	12 (24.5)	13 (25.5)	
Congestive heart failure, %	12 (24.5)	10 (19.6)	
Vertebral compression fracture, %	11 (22.4)	9 (17.6)	
Cataract, %	6 (12.2)	5 (9.8)	
Chronic obstructive pulmonary disease, %	6 (12.2)	3 (5.9)	
Old myocardial infarction, %	5 (10.2)	5 (9.8)	
Malignancy, %	4 (8.1)	5 (9.8)	
Benign prostatic hyperplasia, %	5 (10.2)	3 (5.9)	
White blood cells, counts/μl	5796 ± 398	6101 ± 431	0.15
Hemoglobin, g/dl	11.8 ± 0.4	12.2 ± 0.4	0.09
Platelets, $\times 10^4$ counts/μl	23.6 ± 2.2	22.8 ± 2.0	0.28
Albumin, g/dl	3.7 ± 0.1	3.7 ± 0.1	0.35
AST, IU/l	20.7 ± 2.0	21.1 ± 2.9	0.40
ALT, IU/l	12.9 ± 2.0	13.5 ± 2.5	0.35
BUN, mg/dl	17.6 ± 1.0	16.5 ± 1.3	0.10
Creatinine, mg/dl	0.68 ± 0.5	0.70 ± 0.5	0.25

Data are presented as mean ± SD (standard deviation) unless otherwise indicated.
[a] 23-valent pneumococcal polysaccharide vaccine.
[b] 7-valent pneumococcal conjugate vaccine.

90s and 3 subjects who were 101 years old. The majority (77%) of the subjects were female. There were no significant differences in major co-morbidities between the PPV23 group and the PCV7 group. No other significant differences in laboratory data were observed between the two groups. All the participants from both groups received routine immunization against seasonal influenza.

3.2. Immunogenicity: levels of serotype-specific IgG

Data for the GMCs of serotype-specific IgG responses before and one month after vaccination with PPV23 or PCV7 are summarized in Table 2 and presented graphically in Fig. 2. The original data on serotype-specific IgG are also shown in Supplementary Table 1. No significant differences of baseline serotype-specific IgG GMCs were observed between the two groups for all serotypes measured. In both groups, significant increases in IgG GMCs were observed from baseline to one month following the initial dose for all seven serotypes evaluated. The GMCs of serotype-specific IgGs for serotypes 4, 9V, 18C, and 23F of the study subjects were significantly more elevated in the PCV7 group than in the PPV23 group.

3.3. Immunogenicity: OI

Data for the GMTs of serotype-specific OIs before and one month after vaccination with PPV23 or PCV7 are summarized in Table 3 and presented graphically in Fig. 3. The original data on serotype-specific OIs are also shown in Supplementary Table 2. No significant differences in the baseline GMTs of serotype-specific OIs were observed between the two groups for all serotypes measured. In both groups, significant increases in the GMTs of OIs were observed from baseline to one month following the initial dose for all seven serotypes evaluated. The GMTs of serotype-specific OIs for serotypes 4, 9V, 18C, and 23F of the study subjects were significantly elevated in the PCV7 group compared to the PPV23 group.

3.4. Safety

Both vaccines were tolerated without any severe adverse events. No differences were observed in systemic side effects between the two groups; however, local side effects such as redness and localized swelling were more commonly observed in the PCV7 group (Table 4). No participants required unscheduled medical examinations within the first 7 days after vaccination.

4. Discussion

The current study is the first to demonstrate pneumococcal vaccine responses in pneumococcus vaccine-naïve elderly people (at or over 80 years of age) by evaluating serotype-specific IgG antibodies and serotype-specific OIs between PPV23 and PCV7. Our major findings are that both PPV23 and PCV7 elicited increases in IgG and OI, and that PCV7 is more potent than PPV23 in terms of its immunogenicity against four out of seven serotypes included in PCV7. We also demonstrated the safety of these preparations in these elderly individuals, with no serious adverse effects observed in either group.

We believe that there are several important strengths of this study. One of them is that not only serotype-specific IgG levels but also serotype-specific OIs were evaluated. Due to technical difficulties with OI assays, OI measurements have been reported in only a limited number of clinical studies to date. However, we were able to evaluate functional antibodies, which are superior surrogate markers for protection against pneumococcal pneumonia and bacteremia, by utilizing the latest generation of ELISA methodology [12].

Another important strength of this study is the age distribution of the participants, considering the current inevitable tendency toward increasing longevity in humans. Since the host response induced by vaccinations varies depending on the age of the recipient, the development of safe and effective vaccinations for the elderly is clinically important.

In our study, antibodies against serotypes 4, 9V, 18C, and 23F were significantly elevated in the study subjects. These data were consistent with a previous study indicating that serotype-specific IgG levels of 4, 6B, 9V, 14, 18C, and 23F, and serotype-specific OIs of 4, 9V, 14, 18C, and 23F were significantly elevated in the PCV7 group consisting of elderly people more than 70 years old [2]. In addition, in accordance with our data, they reported that serotype 6B and 19F did not show superior immunogenicity compared with other serotypes in elderly people.

In several studies, 1.0-mL doses of PCV7 were administered [5,13]. However, we used half this dosage in our clinical study to minimize potential adverse effects. In fact, both PPV23 and PCV7 were tolerated by the participants and were associated with few local reactions or systemic adverse effects. No severe adverse effects were observed in either group. A higher frequency of local reactions was observed in the PCV7 group compared with the PPV23 group, although we were unable to determine if this increase was caused by the conjugation specifically. According to a dose-range study of pneumococcal conjugate vaccine reported by Lode et al. [14], both serotype-specific IgG and OI displayed increases in dose-dependent manners, although local reactions for the double dose were not statistically higher than for the single dose. Based on this notion, in our study, 1.0-mL injections rather than

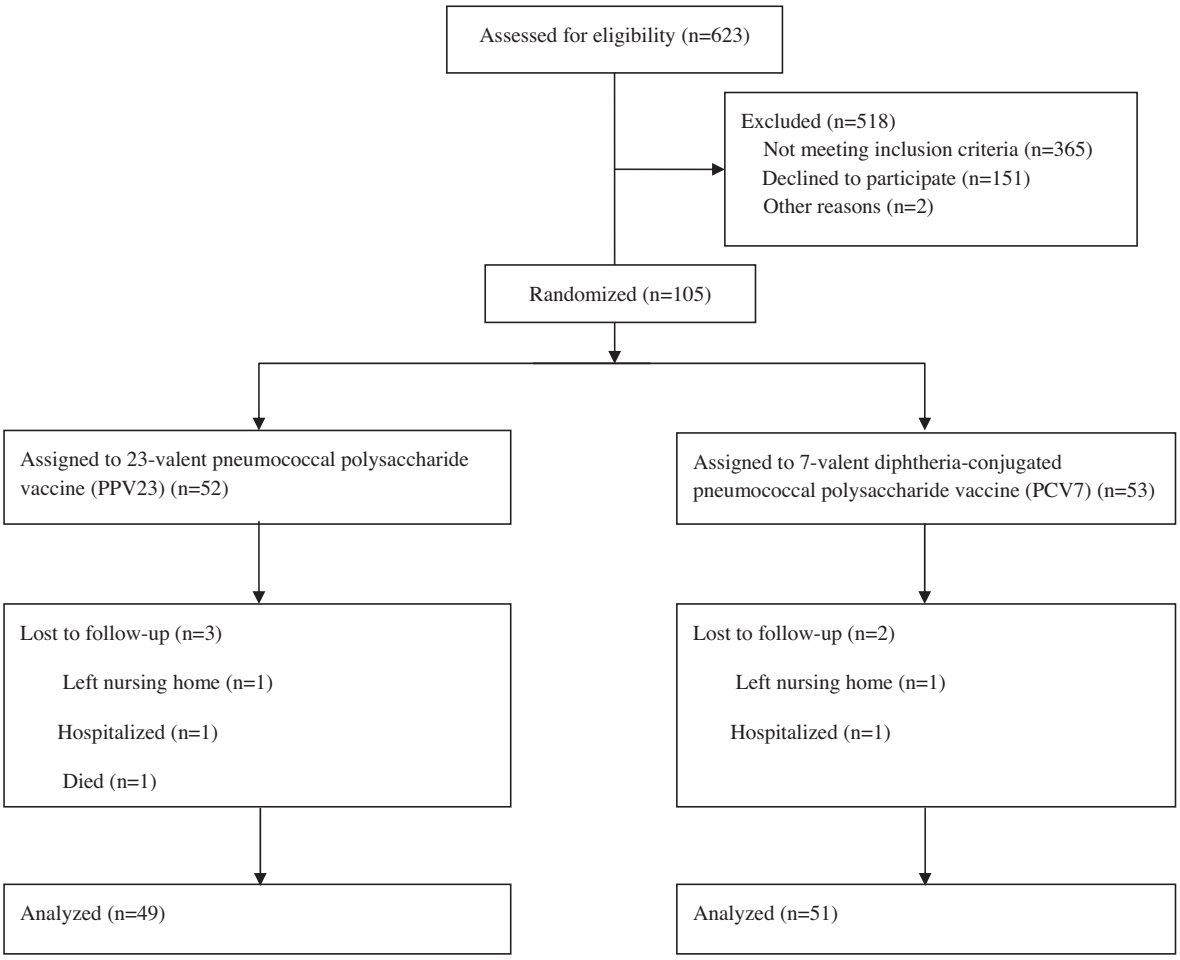

Fig. 1. Flow diagram of trial.

0.5-mL injections of PCV7 could have safely obtained more potent immunogenicity.

The mean number of co-morbidities of study participants staying at nursing homes was 3.34 in our study. According to the nationwide epidemiological study in Scotland by Barnett K et al., the mean number of co-morbidities is 2.60 in elderly people aged 65–84 years and 3.62 in elderly people aged 85 and over [15]. The cross sectional study of aged Medicare beneficiaries in the United States shows that the mean number of co-morbidities is 2.71 in elderly people aged 80 and over [16]. Considering these previous data, our study population of nursing homes could be regarded as not an unusual population of the elderly people in the developed countries.

This study has several limitations. Firstly, a vaccine type and an injection route have to be considered. In this study, we could not use PCV13 because of the lack of the license in Japan at the time of the current study, while PCV13 was launched in Japan in 2014. Therefore our study is out-of-date data at the present. Although PCV is usually administered intramuscularly, not subcutaneously, an intramuscular injection of PCV7 was not allowed in Japan at the time of our clinical study. In order to minimize injection dependent bias, we administered PCV7 subcutaneously by following that the most common route of PPV23 is the subcutaneous route in Japan. Even though, we should have administered both PPV23 and PCV7 intramuscularly.

Table 2
The geometric mean concentrations of serotype-specific IgG antibody before and one month after vaccination pneumococcal vaccines.

Serotype	Pre IgG μg/ml (95% CI)		Post IgG μg/ml (95% CI)		Bonferroni-adjusted *P* value
	PPV23[a] (*n* = 49)	PCV7[b] (*n* = 51)	PPV23 (*n* = 49)	PCV7 (*n* = 51)	
4*	0.44 (0.35–0.55)	0.52 (0.42–0.66)	1.02 (0.77–1.34)	3.38 (2.32–4.92)*	>0.001
6B	1.22 (1.00–1.64)	1.11 (0.84–1.39)	3.51 (2.66–5.30)	3.32 (2.08–4.84)	6.205
9V*	1.03 (0.81–1.38)	0.92 (0.70–1.18)	4.01 (3.12–5.66)	8.75 (5.80–12.14)*	0.003
14	1.88 (1.44–2.85)	2.26 (1.61–3.22)	7.66 (5.00–14.02)	11.41 (7.57–18.26)	3.723
18C*	1.12 (0.89–1.56)	1.08 (0.80–1.39)	4.93 (3.53–6.76)	10.02 (6.98–14.39)*	0.043
19F	1.69 (1.38–2.15)	2.24 (1.72–2.82)	5.26 (3.65–7.30)	6.10 (4.08–8.45)	2.467
23F*	1.28 (0.95–1.81)	1.31 (0.95–1.80)	5.39 (3.51–8.98)	14.68 (9.75–22.04)*	0.014

[a] 23-valent pneumococcal polysaccharide vaccine.
[b] 7-valent pneumococcal conjugate vaccine.
* A significant difference in absolute postvaccination IgG levels between vaccine groups.
Within each study group, postvaccination antibody levels were higher than baseline ($P < 0.01$) for all serotypes.

Table 3
The geometric mean titers of serotype-specific opsonization index before and one month after vaccination pneumococcal vaccines.

Serotype	Pre OI[a] (95% CI)		Post OI (95% CI)		Bonferroni-adjusted *P* value
	PPV23[b] (*n* = 49)	PCV7[c] (*n* = 51)	PPV23 (*n* = 49)	PCV7 (*n* = 51)	
4*	3.55 (2.55–5.22)	5.77 (3.53–9.44)	45.84 (25.55–104.83)	**710.65*** (307.45–1642.62)*	0.005
6B	17.97 (10.58–38.69)	23.34 (12.10–40.88)	271.51 (123.06–586.19)	700.27 (327.87–1188.63)	2.227
9V*	24.44 (13.77–49.77)	19.34 (9.97–34.30)	234.47 (138.37–478.25)	**958.78*** (559.49–1680.79)*	0.012
14	44.83 (24.67–101.30)	90.57 (38.43–183.84)	588.67 (262.75–1380.93)	1925.23 (1144.17–3430.09)	2.259
18C*	47.67 (25.48–89.65)	39.13 (19.53–69.75)	708.20 (329.96–1295.19)	**2730.37*** (1805.42–4118.33)*	0.016
19F	18.26 (10.23–32.94)	25.94 (13.43–45.32)	352.42 (163.69–628.10)	414.32 (196.85–707.47)	3.572
23F*	19.00 (10.50–35.76)	14.51 (7.30–26.69)	197.51 (80.78–466.58)	**2076.51*** (1129.01–3937.53)*	>0.001

[a] Opsonization index.
[b] 23-valent pneumococcal polysaccharide vaccine.
[c] 7-valent pneumococcal conjugate vaccine.
* Bolded items represent a significant difference in absolute postvaccination OI levels between vaccine groups.
Within each study group, postvaccination OI were higher than baseline ($P < 0.01$) for all serotypes.

Another limitation is that it was only one month after vaccination that the antibody levels were examined, thereby limiting our knowledge regarding long-term effects. Our recent study suggested sustained levels of serotype-specific IgG and OI after primary and secondary vaccination with PPV23 among elderly individuals with chronic lung diseases [17]. We therefore intend to compare the serotype-specific IgG and OI after primary vaccination between the study subjects immunized with PPV23 and PCV7 in this study.

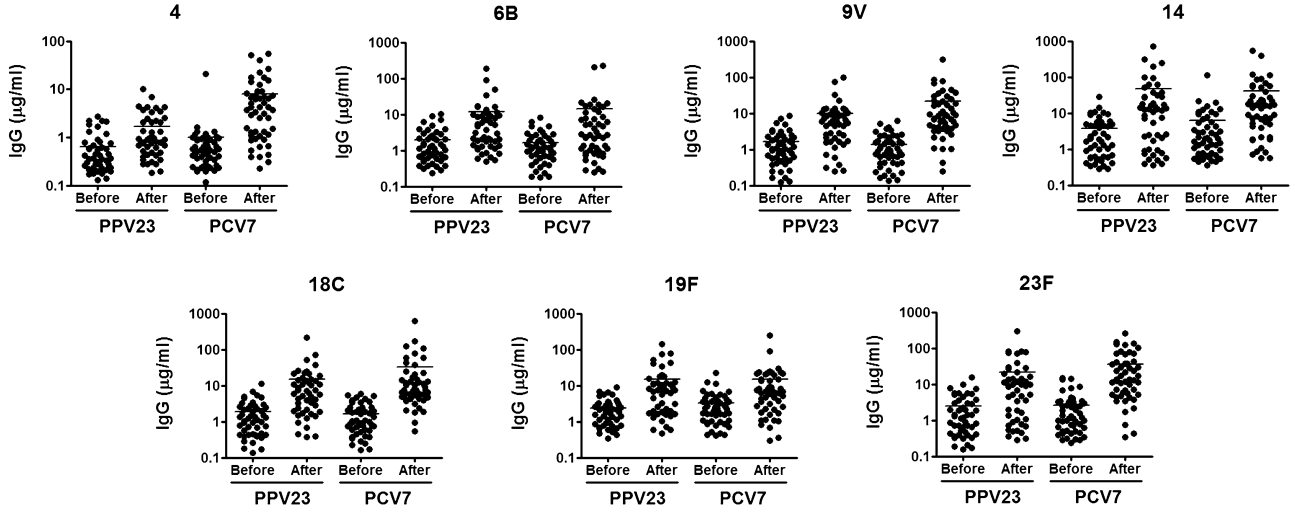

Fig. 2. The serotype-specific baseline and 1-month absolute IgG antibody levels are shown for each patient. The heptavalent diphtheria-conjugated pneumococcal polysaccharide vaccine (PCV7) resulted in statistically significantly higher antibody levels at one month to baseline for serotypes 4, 9V, 18C and 23F.

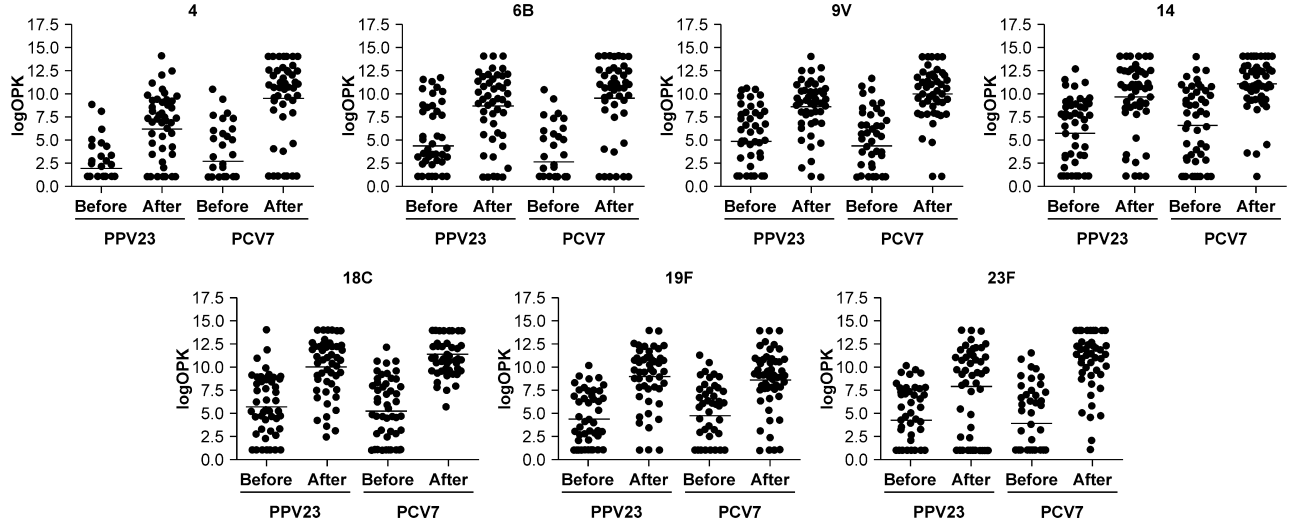

Fig. 3. The serotype-specific baseline and one-month geometric mean opsonophagocytic killing index are shown for each patient. The heptavalent diphtheria-conjugated pneumococcal polysaccharide vaccine (PCV7) resulted in statistically significantly higher geometric mean opsonophagocytic killing index at one month to baseline for serotypes 4, 9V, 18C and 23F.

Table 4
Comparison of adverse reactions among elderly individuals after vaccination with pneumococcal vaccines.

Characteristics	PPV23[a] (n = 49)	PCV7[b] (n = 51)	P value
Fatigue			
Grade I	3	3	0.96
Grade II	0	0	–
Muscle aches			
Grade I	0	0	–
Grade II	0	0	–
Headache			
Grade I	0	0	–
Grade II	0	0	–
Itching of vaccinated arm			
Grade I	2	4	0.43
Grade II	0	0	–
Pain of vaccinated arm			
Grade I	0	0	–
Grade II	0	0	–
Fever			
Grade I	4	3	0.65
Grade II	0	0	–
Redness			
Grade I (<8 cm)	9	16	0.13
Grade II (>8 cm and <15 cm)	3	5	0.50
Grade III (>15 cm)	0	0	–
Localized swelling			
Grade I (<8 cm)	11	19	0.11
Grade II (>8 cm and <15 cm)	0	0	–

[a] 23-valent pneumococcal polysaccharide vaccine.
[b] 7-valent pneumococcal conjugate vaccine.

There are several unsolved issues for pneumococcal vaccination. The titer of correlate of protection for adults who received pneumococcal vaccines has not yet been established, while a titer of 0.35 μg/mL has been defined as a correlate of protection against invasive diseases among infants who received the pneumococcal conjugate vaccine. In this respect, as for adults, the advantage of the higher immunogenicity in the PCV7 group is not clear in protection against pneumococcal diseases. Moreover, the difference of the serotypes covering range by each pneumococcal vaccine has to be taken into consideration. Based on the newest domestic reports on the serotype distribution of community-acquired pneumonia (CAP) [18] and invasive pneumococcal disease (IPD) [19], the ratio of serotypes of CAP covered by PPV23, PCV7 and PCV13 are 82.5%, 61.4% and 83.3% while the ratio of serotypes of IPD covered by PPV23, PCV7 and PCV13 are 85.4%, 39.8% and 61.9%, respectively. Taken together, to make best of our current study, the nationwide surveillance of *S. pneumoniae* infections is essential in Japan. Beyond the scope of this current study, the most important aspect is to establish the vaccine policy which produce clinical efficacy for preventing *S. pneumoniae* infections.

In conclusion, we demonstrated higher increases in the GMCs of serotype-specific IgG levels and the GMTs of OIs in the PCV7 group compared to the PPV23 group, and confirmed the safety of vaccinations with PCV7 and PPV23 for subjects aged 80 years and older.

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Conflict of interest: Dr. Hasegawa has received grants from MSD and Pfizer.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.11.023.

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