HUMAN VACCINES & IMMUNOTHERAPEUTICS
2018, VOL. 14, NO. 8, 1931–1938
https://doi.org/10.1080/21645515.2018.1456611

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RESEARCH PAPER

Time interval of revaccination with 23-valent pneumococcal polysaccharide vaccine more than 5 years does not affect the immunogenicity and safety in the Japanese elderly

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ABSTRACT

In the previous study, revaccination with 23-valent pneumococcal polysaccharide vaccine (PPSV23) in a total of 161 elderly subjects (≥70 years of age) who had received the initial vaccination at least 5 years before (range: 5 to11 years) showed an acceptable safety profile and induction of immune responses to the serotypes in PPSV23. The optimal interval between the initial vaccination and revaccination with PPSV23 is of interest to protect elderly from pneumococcal disease over the long-term. In this post-hoc analysis, we analyzed that the immunogenicity and safety of revaccination with PPSV23 by time interval after the initial vaccination. The level of serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMCs) and opsonophagocytic killing activity (OPA) geometric mean titers (GMTs) at 4 weeks after revaccination with PPSV23 in each subgroup based on time interval (5, 6, 7, 8 and 9–11 years) after the initial vaccination were comparable to those after the primary vaccination and vaccine-induced serotype-specific IgG and OPA levels were similar regardless of the time interval after the initial vaccination. There was no difference in the safety profiles among the subgroups. In conclusion, administration of a second dose of PPSV23 at least 5 years after the initial vaccination was immunogenic and well-tolerated in the elderly ≥70 years of age regardless of the time interval after the initial vaccination.

ARTICLE HISTORY
Received 9 January 2018
Revised 7 March 2018
Accepted 17 March 2018

KEYWORDS
23-valent pneumococcal polysaccharide vaccine; revaccination; time interval; immunogenicity

Introduction

Streptococcus pneumoniae is a leading microorganism of community-acquired pneumonia (CAP) worldwide, and morbidity and mortality of pneumococcal pneumonia increase rapidly particularly in adults ≥65 years of age.[1-3] Pneumococcal vaccines have been shown to be effective to prevent pneumococcal diseases caused by the serotypes in the pneumococcal vaccines.

Two pneumococcal vaccines have been licensed for adults in Japan as of 2018. The 23-valent pneumococcal polysaccharide vaccine (PPSV23; Pneumovax®NP Merck & Co., Inc., Kenilworth, NJ, USA), which elicits T-cell independent immune responses, is indicated in persons aged ≥2 years old who are at increased risk of pneumococcal disease, including such as those with sickle cell and functional or anatomic asplenia, chronic lung/heart disease, renal and hepatic dysfunction or diabetes, as well as all adults ≥65 years of age. The 13-valent pneumococcal conjugate vaccine (PCV13; Pvenevar13® Pfizer Inc., New York, USA), which elicits T-cell dependent immune responses, is indicated in children 2 months through 6 years of age and all adults ≥65 years of age. In Japan, PPSV23 was introduced in the national immunization program (NIP) on October 1, 2014 as a single administration with PPSV23 in adults aged 65 years old who have not received PPSV23 before. Elderly adults aged 70, 75, 80, 85, 90, 95 and 100 years old are also eligible for NIP from fiscal year 2014 to 2018 as a catch-up program (Elderly adults aged 65, 70, 75, 80, 85, 90, 95 and 100 years and older are eligible only for fiscal year 2014).

Following single vaccination with PPSV23, serotype-specific immunoglobulin G (IgG) concentrations and opsonophagocytic killing activity (OPA) titers increase and then decline over time, which may lead to an increased risk of pneumococcal disease. Therefore, revaccination with PPSV23 is desired to provide continued prevention against pneumococcal pneumonia in an aging population. Over the last century, life expectancy has increased worldwide, especially in Japan where approximately 30% of people were ≥65 years of age in 2016.[4] Although the effectiveness of revaccination with PPSV23 is not established so far, the immunogenicity and safety of repeat vaccination with PPSV23 in adults has been investigated.[5-11] A recent clinical study demonstrated that revaccination with PPSV23 in U.S adults aged 50 years and older induced significant increases in serotype-specific IgG concentrations and OPA titers.[5-7] These results were confirmed in our previous study in which revaccination of adults ≥70 years of age with PPSV23 was associated with an increase in serotype-specific IgG and OPA and levels measured following revaccination

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were generally comparable to those observed after primary vaccination with PPSV23.[12] However, the elevated IgG and OPA levels after primary or revaccination with PPSV23 declined over time though remaining above levels measured in vaccine-naïve subjects. The levels of IgG at 5 years after revaccination were similar to those at 5 years after the primary vaccination.[7] Hammitt et al. reported that repeat revaccination with PPSV23 at an interval of six or more years was immunogenic and generally well-tolerated in adults aged 50−74 years living in Alaska.[8]

Revaccination with PPSV23 in older adults has been introduced in NIP in Germany[13] and Philippines.[14] To date, revaccination with PPSV23 is not introduced in NIP for older adults in Japan. In our previous study, we showed that revaccination with PPSV23 at least 5 years after the initial dose is immunogenic and well-tolerated. However, questions have remained on the optimal administration interval for sufficient immune response between the revaccination and the initial vaccination with PPSV23. In this post-hoc analysis we examined the immunogenicity and safety of PPSV23 revaccination by time interval after the initial vaccination with PPSV23 in the Japanese elderly.

Results

Participant accounting and demographics

This report is a post-hoc analysis from the PPSV23 revaccination study with Japanese adults ≥70 years of age.[12] A total of 161 subjects with a history of prior vaccination with PPSV23 were enrolled into revaccination group and 81 subjects who were naïve to PPSV23 were enrolled into the primary vaccination group. All subjects who received a single dose of PPSV23 in both groups were included in the post-hoc analysis. Baseline characteristic in the revaccination subgroup by time interval after the initial vaccination with PPSV23 is shown in Table 1. Number of revaccinated subjects at an interval of 5, 6, 7, 8 and 9–11 years were 46 (29%), 31 (19%), 40 (25%), 20 (12%) and 24 (15%), respectively. The percentages of males were comparable among the revaccination subgroups by time interval. Mean age of subjects with an interval of 5, 6, 7, 8 and 9–11 years were 76.8, 78.8, 80.3, 79.1 and 79.9 years old, respectively. Most revaccinated subjects had any underlying medical conditions (at least 1 of chronic heart disease, chronic lung disease and diabetes mellitus). The distribution of chronic heart disease among the revaccination subgroups was imbalanced, but the other underlying medical condition, the number of underlying medical condition and gender were comparable among the revaccination subgroups.

Immunogenicity

Serotype-specific IgG

Serotype-specific IgG geometric mean concentrations (GMCs) to 14 serotypes measured at baseline and 4 weeks after vaccination with PPSV23 in the primary vaccination group and revaccination subgroups at each time interval after the initial vaccination are presented in Table 2. In all revaccination subgroups, baseline serotype-specific IgG GMCs to 14 serotypes were higher compared to those in the primary vaccination and these levels were comparable among the revaccination subgroups. Following revaccination with PPSV23, serotype-specific IgG GMCs to 14 serotypes increased from baseline in all revaccination subgroups. Although IgG geometric means fold rises (GMFRs) in all revaccination subgroups were lower than those in the primary vaccination group, the lower bound of 95% confidence intervals (CIs) of GMFRs for 14 serotypes were above >1 in all revaccination subgroups. There were variabilities in serotype-specific IgG GMCs measured at 4 weeks after vaccination with PPSV23 between the primary vaccination group and revaccination subgroups, however 95% CIs of postvaccination IgG GMCs in each revaccination subgroup and primary vaccination group overlapped for all serotypes (Fig. 1).

Serotype-specific OPA

For most serotypes tested, baseline serotype-specific OPA geometric mean titers (GMTs) in all revaccination subgroups were generally higher than those in the primary vaccination, except for serotype 22F in the revaccination subgroup at an interval of 9–11 years (Table 3). Following vaccination with PPSV23, serotype-specific OPA GMTs increased from baseline for all 6 tested serotypes in all revaccination subgroups. Similar to IgG responses and although OPA GMFRs in all revaccination

Table 1. Baseline characteristics.

	Revaccination with PPSV23 (N = 161) Subgroups by time interval after the initial vaccination				
	5 years (N = 46) n (%)	6 years (N = 31) n (%)	7 years (N = 40) n (%)	8 years (N = 20) n (%)	9–11 years (N = 24) n (%)
Gender					
Male	18 (39.1)	12 (38.7)	16 (40.0)	10 (50.0)	11 (45.8)
Female	28 (60.9)	19 (61.3)	24 (60.0)	10 (50.0)	13 (54.2)
Mean of age, years (SD)	76.8 (4.8)	78.8 (4.4)	80.3 (4.8)	79.1 (4.9)	79.9 (3.9)
Underlying medical condition					
Chronic heart disease	31 (67.4)	19 (61.3)	37 (92.5)	18 (90.0)	22 (91.7)
Chronic lung disease	21 (45.7)	11 (35.5)	9 (22.5)	7 (35.0)	5 (20.8)
Diabetes mellitus	12 (26.1)	1 (3.2)	11 (27.5)	5 (25.0)	4 (16.7)
Number of underlying medical condition					
0	8 (17.4)	6 (19.4)	2 (5.0)	1 (5.0)	2 (8.3)
1	17 (37.0)	19 (61.3)	20 (50.0)	9 (45.0)	14 (58.3)
≥2	21 (45.7)	6 (19.4)	18 (45.0)	10 (50.0)	8 (33.3)

N: number of subjects in the vaccination group; n: number of subjects in the indicated category; SD: standard deviation

Table 2. Serotype-specific IgG GMCs and GMFR before and after primary vaccination and revaccination with PPSV23 by time interval after the initial vaccination.

			Revaccination with PPSV23				
Serotype		Primary vaccination (N=81) GMCs (95%CI)	5 years (N=46) GMCs (95%CI)	6 years (N=31) GMCs (95%CI)	7 years (N=40) GMCs (95%CI)	8 years (N=20) GMCs (95%CI)	9–11 years (N=24) GMCs (95%CI)
1	Baseline	0.43 (0.33,0.56)	1.30 (0.85, 2.01)	0.88 (0.54, 1.46)	0.85 (0.64, 1.14)	0.86 (0.51, 1.45)	0.76 (0.42, 1.36)
	After vaccination	4.30 (3.14,5.89)	3.00 (1.95, 4.60)	3.21 (1.94, 5.31)	2.94 (2.06, 4.19)	6.73 (3.77, 12.01)	2.81 (1.61, 4.91)
	GMFR	10.01 (7.67,13.07)	2.30 (1.86, 2.84)	3.63 (2.55, 5.17)	3.45 (2.48, 4.80)	7.82 (4.59, 13.32)	3.70 (2.26, 6.08)
3	Baseline	0.09 (0.07,0.11)	0.16 (0.12, 0.20)	0.10 (0.07, 0.14)	0.18 (0.12, 0.26)	0.12 (0.08, 0.19)	0.12 (0.07, 0.20)
	After vaccination	0.54 (0.42,0.69)	0.49 (0.35, 0.69)	0.38 (0.26, 0.55)	0.49 (0.32, 0.75)	0.59 (0.34, 1.02)	0.58 (0.32, 1.08)
	GMFR	4.01 (3.17,5.08)	2.68 (2.05, 3.50)	2.53 (1.78, 3.58)	2.26 (1.73, 2.95)	3.48 (2.27, 5.35)	3.39 (2.15, 5.35)
4	Baseline	0.15 (0.12,0.18)	0.29 (0.20, 0.42)	0.23 (0.14, 0.38)	0.29 (0.19, 0.44)	0.23 (0.12, 0.41)	0.33 (0.17, 0.62)
	After vaccination	0.90 (0.67,1.22)	0.59 (0.39, 0.88)	0.55 (0.32, 0.94)	0.57 (0.36, 0.89)	0.64 (0.33, 1.22)	1.03 (0.48, 2.23)
	GMFR	5.84 (4.56,7.47)	1.99 (1.65, 2.41)	2.36 (1.74, 3.20)	1.90 (1.55, 2.32)	2.72 (2.06, 3.59)	2.98 (1.88, 4.72)
5	Baseline	0.65 (0.53,0.80)	1.11 (0.79, 1.55)	1.30 (0.75, 2.25)	1.37 (0.92, 2.04)	1.30 (0.75, 2.26)	1.84 (1.06, 3.17)
	After vaccination	2.42 (1.83,3.20)	1.84 (1.28, 2.65)	2.61 (1.45, 4.70)	2.23 (1.52, 3.27)	3.39 (1.71, 6.71)	4.81 (2.73, 8.50)
	GMFR	3.73 (2.92,4.76)	1.66 (1.38, 2.01)	2.00 (1.48, 2.71)	1.63 (1.41, 1.88)	2.60 (1.80, 3.77)	2.62 (1.79, 3.82)
6B	Baseline	0.33 (0.24,0.44)	0.77 (0.48, 1.24)	1.15 (0.71, 1.87)	1.18 (0.74, 1.88)	0.77 (0.44, 1.37)	0.62 (0.32, 1.17)
	After vaccination	2.08 (1.41,3.07)	1.52 (0.95, 2.42)	2.50 (1.49, 4.22)	2.67 (1.62, 4.40)	1.79 (0.92, 3.48)	2.40 (1.14, 5.07)
	GMFR	5.83 (4.41,7.69)	1.85 (1.53, 2.24)	2.14 (1.66, 2.75)	2.27 (1.76, 2.92)	2.32 (1.56, 3.44)	3.57 (2.54, 5.02)
7F	Baseline	0.34 (0.25,0.46)	0.92 (0.60, 1.43)	0.74 (0.42, 1.32)	0.86 (0.51, 1.44)	1.06 (0.50, 2.27)	0.71 (0.40, 1.25)
	After vaccination	3.36 (2.29,4.92)	2.17 (1.39, 3.40)	1.94 (1.12, 3.34)	2.73 (1.65, 4.50)	4.95 (2.36, 10.38)	2.51 (1.50, 4.20)
	GMFR	8.92 (6.83,11.64)	2.25 (1.78, 2.83)	2.39 (1.86, 3.08)	3.02 (2.38, 3.83)	4.49 (2.88, 7.01)	3.53 (2.47, 5.03)
9V	Baseline	0.38 (0.28,0.50)	0.86 (0.56, 1.32)	0.78 (0.50, 1.21)	1.13 (0.77, 1.66)	0.85 (0.47, 1.53)	0.79 (0.48, 1.33)
	After vaccination	2.55 (1.86,3.49)	1.85 (1.21, 2.84)	1.69 (1.09, 2.64)	2.33 (1.58, 3.44)	2.86 (1.67, 4.91)	2.12 (1.16, 3.85)
	GMFR	6.65 (5.29,8.37)	2.16 (1.80, 2.59)	2.17 (1.68, 2.80)	2.06 (1.73, 2.45)	3.38 (2.33, 4.88)	2.66 (2.05, 3.45)
14	Baseline	1.30 (0.96,1.76)	3.24 (2.05, 5.14)	3.61 (2.05, 6.36)	4.25 (2.81, 6.43)	7.78 (3.99, 15.19)	2.36 (1.14, 4.89)
	After vaccination	5.34 (3.63,7.84)	4.59 (2.97, 7.08)	6.22 (3.28, 11.79)	6.91 (4.63, 10.32)	17.05 (8.69, 33.45)	4.73 (2.36, 9.47)
	GMFR	4.07 (3.09,5.37)	1.41 (1.19, 1.68)	1.72 (1.20, 2.47)	1.63 (1.28, 2.08)	2.19 (1.45, 3.30)	1.95 (1.43, 2.66)
18C	Baseline	0.65 (0.50,0.84)	1.42 (0.91, 2.23)	1.73 (1.14, 2.62)	2.10 (1.51, 2.93)	2.15 (1.23, 3.75)	1.64 (0.97, 2.75)
	After vaccination	4.98 (3.72,6.66)	2.74 (1.74, 4.31)	3.88 (2.64, 5.70)	5.11 (3.79, 6.87)	6.81 (4.04, 11.49)	4.70 (2.59, 8.55)
	GMFR	7.71 (6.11,9.73)	1.90 (1.55, 2.33)	2.24 (1.73, 2.92)	2.43 (1.89, 3.12)	3.17 (2.17, 4.64)	2.87 (2.00, 4.12)
19A	Baseline	1.47 (1.15,1.88)	1.75 (1.15, 2.65)	2.21 (1.37, 3.57)	2.53 (1.79, 3.57)	1.91 (1.10, 3.31)	2.56 (1.71, 3.83)
	After vaccination	6.61 (4.79,9.12)	3.06 (1.92, 4.87)	4.64 (2.81, 7.64)	4.34 (2.95, 6.39)	6.36 (3.15, 12.83)	6.54 (3.95, 10.83)
	GMFR	4.49 (3.53,5.71)	1.75 (1.43, 2.15)	2.10 (1.57, 2.80)	1.72 (1.43, 2.05)	3.32 (2.31, 4.78)	2.56 (1.99, 3.29)
19F	Baseline	0.61 (0.46,0.80)	1.12 (0.69, 1.81)	1.54 (0.96, 2.47)	1.98 (1.28, 3.07)	2.05 (0.94, 4.45)	1.80 (1.14, 2.86)
	After vaccination	3.90 (2.83,5.38)	2.34 (1.39, 3.93)	3.33 (1.93, 5.73)	4.63 (2.98, 7.18)	7.14 (3.16, 16.15)	7.41 (4.26, 12.88)
	GMFR	6.25 (5.02,7.77)	2.06 (1.65, 2.58)	2.16 (1.67, 2.79)	2.33 (1.84, 2.96)	3.36 (2.43, 4.66)	4.11 (3.01, 5.61)
22F	Baseline	0.21 (0.16,0.26)	0.51 (0.34, 0.75)	0.61 (0.36, 1.06)	0.51 (0.33, 0.79)	0.67 (0.35, 1.28)	0.51 (0.28, 0.94)
	After vaccination	1.15 (0.83,1.58)	1.53 (1.01, 2.31)	1.40 (0.79, 2.47)	1.31 (0.84, 2.05)	3.09 (1.38, 6.92)	1.57 (0.92, 2.70)
	GMFR	4.94 (3.82,6.39)	2.91 (2.17, 3.89)	2.17 (1.53, 3.09)	2.49 (1.90, 3.26)	4.49 (2.76, 7.29)	2.92 (2.23, 3.82)
23F	Baseline	0.50 (0.37,0.68)	1.37 (0.85, 2.21)	1.32 (0.90, 1.92)	1.39 (0.84, 2.31)	1.87 (0.93, 3.76)	1.05 (0.52, 2.13)
	After vaccination	3.23 (2.18,4.78)	2.75 (1.64, 4.62)	3.16 (2.04, 4.91)	3.47 (2.11, 5.71)	6.43 (3.20, 12.93)	2.84 (1.41, 5.70)
	GMFR	6.11 (4.65,8.02)	1.92 (1.52, 2.42)	2.40 (1.88, 3.06)	2.45 (1.88, 3.20)	3.93 (2.57, 6.03)	2.40 (1.80, 3.20)
33F	Baseline	1.40 (1.11,1.76)	4.49 (2.99, 6.76)	3.78 (2.16, 6.63)	6.67 (4.37, 10.17)	4.35 (2.54, 7.45)	4.73 (2.83, 7.91)
	After vaccination	12.84 (9.52,17.33)	8.47 (5.90, 12.14)	8.23 (5.10, 13.26)	10.86 (7.54, 15.66)	14.39 (7.48, 27.69)	11.01 (7.36, 16.48)
	GMFR	9.11 (7.19,11.56)	1.88 (1.58, 2.25)	2.13 (1.69, 2.68)	1.63 (1.39, 1.90)	3.31 (2.14, 5.10)	2.33 (1.75, 3.09)

N: number of subjects in the vaccination group; GMCs: geometric mean concentrations; GMFR; geometric means fold rise; CI: confidence interval

subgroups were lower than those measured in the primary vaccination group, the lower bound of 95% CIs of GMFR in all revaccination subgroups exceeded 1. The 95% CIs of postvaccination serotype-specific OPA GMTs to all 6 tested serotypes overlapped in each revaccination subgroup and primary vaccination group, except for serotype 4 in the revaccination subgroup at an interval of 5 years (Fig. 2).

Safety

Injection-site and systemic adverse events occurring after vaccination with PPSV23 in each revaccination subgroup and primary vaccination group were summarized in Table 4. The incidences of solicited injection-site AEs reported within 5 days following vaccination were higher in the revaccination subgroups (regardless of time interval) compared to primary vaccination group. Most injection-site AEs were mild to moderate in intensity in primary vaccination group and revaccination subgroups at any time interval. Severe pain, erythema and swelling of >10 cm were reported by ≤10% of subjects among the various revaccination subgroups. The incidences of systemic AEs within 14 days following vaccination were 19.8% in the primary vaccination group and 15.2%, 29.0%, 30.0%, 25.0% and 37.5% in revaccination subgroups (in 5-year, 6-year, 7-year, 8-year and 9 to 11-year interval, respectively). The most common systemic AEs (≥2 events in any groups) observed in revaccination subgroups of any time intervals were diarrhoea, malaise, fever and nasopharyngitis. Higher incidence of fever reported in the revaccination subgroup at 7-year interval (12.5%) and 9 to 11-year interval (16.7%), but most of reported fever were below 38.5°C. One subject in the revaccination at 9 to 11-year interval developed fever ≥38.5°C.

Discussion

To prevent pneumococcal diseases including invasive pneumococcal disease and pneumococcal pneumonia, it is important to maintain a certain levels of IgG concentrations against each

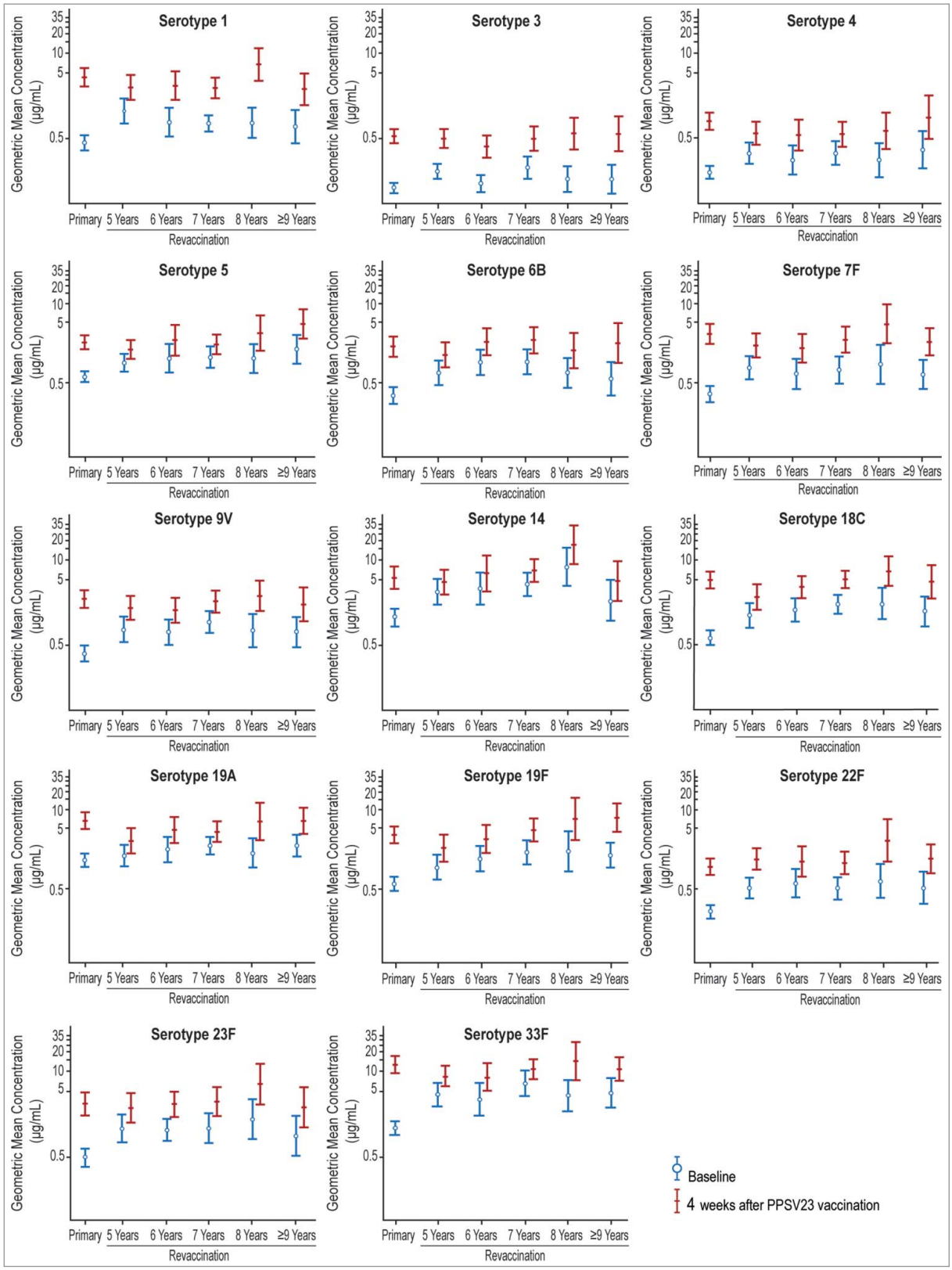

Figure 1. Serotype-specific IgG GMCs and 95% CI for 14 serotypes in the primary vaccination group and revaccination subgroups by time interval. Blue line: IgG GMCs at baseline; Red line: IgG GMCs at 4 weeks after vaccination with PPSV23.

causing serotypes by vaccination, though thresholds of antibody concentrations that correlate with prevention of pneumococcal disease in adults have not been established. Also, the elicited functional OPA antibodies after vaccination are crucial to assess the potential clinical efficacy of a pneumococcal vaccine in adults. The antibody levels after the initial vaccination with PPSV23 gradually waned over time, therefore, revaccination is recommended for persons at increased risk of pneumococcal disease in

Table 3. Serotype-specific OPA GMTs and GMFR before and after primary vaccination and revaccination with PPSV23 by time interval after the initial vaccination.

			Revaccination with PPSV23				
Serotype		Primary vaccination (N = 78–79) GMTs (95%CI)	5 years (N = 45) GMTs (95%CI)	6 years (N = 30–31) GMTs (95%CI)	7 years (N = 38–39) GMTs (95%CI)	8 years (N = 20) GMTs (95%CI)	9–11 years (N = 24) GMTs (95%CI)
3	Baseline	20.41 (15.33,27.18)	23.0 (15.8, 33.4)	24.7 (16.2, 37.7)	36.0 (23.5, 55.1)	26.7 (15.0, 47.5)	40.0 (21.5, 74.3)
	After vaccination	205.18 (162.38,259.28)	134.6 (99.1, 182.9)	130.5 (86.4, 197.2)	164.2 (117.7, 229.2)	212.5 (139.4, 324.0)	255.4 (157.0, 415.4)
	GMFR	8.32 (6.50,10.65)	4.91 (3.69, 6.53)	4.62 (3.24, 6.59)	4.17 (3.11, 5.60)	6.93 (4.31, 11.13)	5.53 (3.59, 8.52)
4	Baseline	15.49 (10.58,22.66)	22.7 (13.6, 38.0)	26.1 (13.4, 50.9)	36.8 (20.9, 64.7)	15.8 (7.5, 33.3)	45.6 (19.2, 108.3)
	After vaccination	351.92 (256.04,483.70)	125.4 (72.0, 218.4)	172.1 (94.8, 312.6)	213.1 (125.1, 363.0)	120.7 (51.1, 284.9)	471.9 (229.1, 972.0)
	GMFR	15.66 (11.08,22.11)	4.52 (2.88, 7.08)	5.05 (3.04, 8.40)	4.75 (2.96, 7.64)	5.40 (2.58, 11.30)	8.46 (4.02, 17.78)
6B	Baseline	47.94 (29.18,78.77)	119.1 (64.5, 219.6)	250.6 (123.9, 506.9)	416.4 (261.2, 664.0)	144.8 (69.0, 304.0)	96.5 (40.7, 229.0)
	After vaccination	746.02 (523.40,1063.33)	379.9 (234.5, 615.5)	686.7 (347.7, 1356.5)	1014.4 (694.4, 1481.7)	511.1 (261.4, 999.2)	595.8 (326.8, 1086.2)
	GMFR	13.55 (9.27,19.81)	2.91 (1.99, 4.25)	2.56 (1.77, 3.70)	2.28 (1.80, 2.88)	3.29 (1.65, 6.57)	5.66 (3.52, 9.10)
14	Baseline	119.21 (75.76,187.60)	301.4 (162.6, 558.7)	309.4 (173.0, 553.4)	544.4 (359.4, 824.7)	656.9 (404.3, 1067.2)	220.7 (103.3, 471.6)
	After vaccination	640.15 (418.65,978.83)	555.3 (331.2, 931.2)	761.4 (416.8, 1390.9)	907.9 (651.7, 1264.8)	1710.2 (973.7, 3003.9)	491.9 (236.5, 1023.0)
	GMFR	5.18 (3.60,7.45)	1.76 (1.33, 2.34)	2.52 (1.67, 3.80)	1.76 (1.38, 2.24)	2.60 (1.65, 4.12)	2.04 (1.38, 3.02)
22F	Baseline	31.43 (18.81,52.52)	76.9 (40.2, 147.2)	158.9 (80.6, 313.3)	123.6 (64.7, 236.1)	52.8 (20.3, 137.4)	30.3 (13.6, 67.9)
	After vaccination	436.97 (289.08,660.52)	599.8 (375.3, 958.4)	692.3 (421.0, 1138.4)	718.9 (442.5, 1168.2)	492.0 (220.0, 1100.3)	335.6 (161.3, 698.0)
	GMFR	10.31 (6.44,16.51)	6.16 (3.67, 10.36)	3.98 (2.51, 6.32)	4.87 (2.94, 8.09)	7.56 (3.28, 17.46)	9.03 (4.50, 18.15)
23F	Baseline	24.30 (15.43,38.28)	90.8 (48.1, 171.3)	100.0 (50.2, 199.0)	112.4 (59.9, 210.7)	144.9 (67.5, 311.0)	142.7 (63.7, 319.9)
	After vaccination	320.39 (206.75,496.49)	195.8 (103.0, 372.1)	280.4 (159.9, 491.9)	397.1 (220.6, 714.7)	593.6 (266.2, 1324.0)	390.8 (187.0, 816.7)
	GMFR	9.77 (6.58,14.51)	1.98 (1.29, 3.05)	2.51 (1.36, 4.62)	2.87 (1.83, 4.48)	3.82 (2.43, 6.02)	2.44 (1.54, 3.88)

N: number of subjects in the vaccination group; GMTs: geometric mean titers; GMFR; geometric means fold rise; CI: confidence interval

the U.S,[15] Germany,[13] UK[16] and Australia.[17] Interval between the initial vaccination and revaccination with PPSV23 should be considered for the safety of revaccination since previous studies reported that high incidences and severity of local injection-site reactions were observed in revaccinated adults within 2 years of their initial vaccination.[18] Jackson et al. reported that no serious vaccine-related adverse events were identified in adults who received a second dose of PPSV23 5 to 13 years after their initial vaccination, and the incidence of the sizable local injection-site reactions (redness and swelling) were higher in the revaccination than in the initial vaccination, but these reactions were resolved within 3 days after revaccination.[19] Therefore, a minimum interval of 5 years between the initial vaccination and revaccination with PPSV23 is definitely recommended to minimize a risk of adverse events following revaccination, however, optimal interval beyond 5 years after the initial vaccination is unclear. This post-hoc analysis showed that baseline serotype-specific IgG GMCs and OPA GMTs to most serotypes in the revaccinated subjects were comparable regardless of the time interval (5, 6, 7, 8 and 9 to 11 years) following their initial vaccination with PPSV23, and remained above levels measured in vaccine-naïve subjects, indicating that the elevated IgG and OPA levels following the initial vaccination with PPSV23 decline over the 5 years postvaccination to reach a steady state over the subsequent 5–

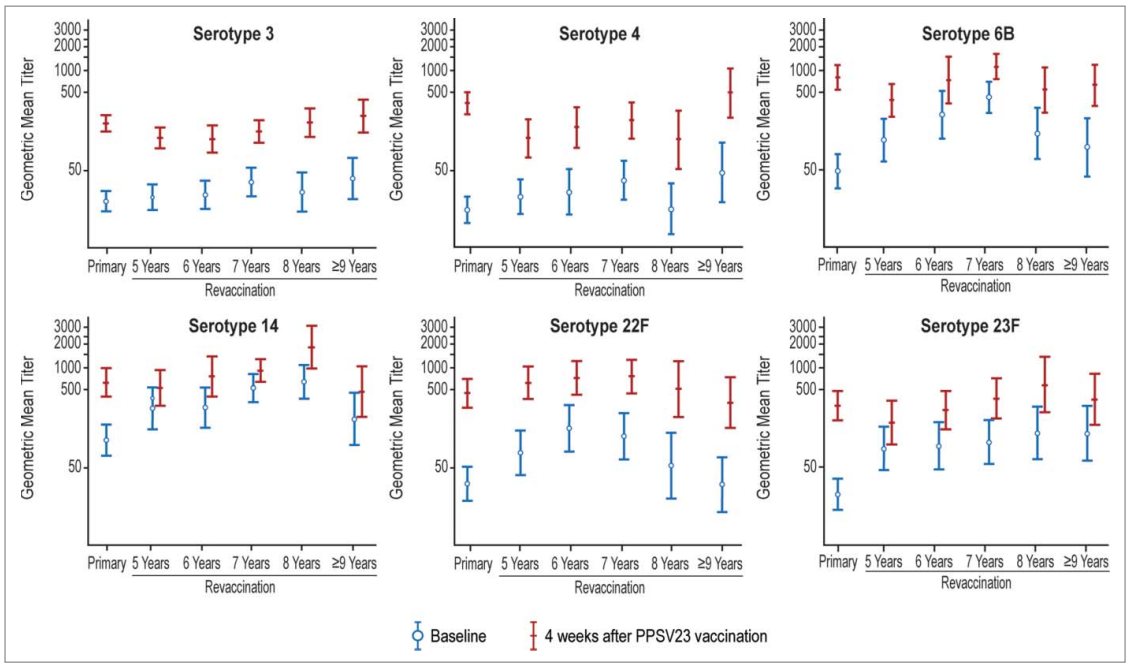

Figure 2. Serotype-specific OPA GMTs and 95% CI for 6 serotypes in the primary vaccination group and revaccination subgroups by time interval. Blue line: OPA GMTs at baseline; Red line: OPA GMTs at 4 weeks after vaccination with PPSV23.

Table 4. Injection-site and systemic AEs after primary vaccination and revaccination with PPSV23 by time interval after the initial vaccination.

		Revaccination with PPSV23				
	Primary vaccination (N = 81) n (%)	5 years (N = 46) n (%)	6 years (N = 31) n (%)	7 years (N = 40) n (%)	8 years (N = 20) n (%)	9-11 years (N = 24) n (%)
Any injection-site AE[#]	41 (50.6%)	34 (73.9)	21 (67.7)	27 (67.5)	18 (90.0)	13 (54.2)
Injection-site pain						
any	38 (46.9)	32 (69.6)	19 (61.3)	24 (60.0)	14 (70.0)	12 (50.0)
Mild	34 (42.0)	28 (60.9)	11 (35.5)	17 (42.5)	12 (60.0)	9 (37.5)
Moderate	4 (4.9)	3 (6.5)	6 (19.4)	5 (12.5)	2 (10.0)	2 (8.3)
Severe	0 (0.0)	1 (2.2)	2 (6.5)	2 (5.0)	0 (0.0)	1 (4.2)
Injection-site erythema (cm)						
any	12 (14.8)	13 (28.3)	13 (41.9)	14 (35.0)	10 (50.0)	7 (29.2)
0 to ≤5	10 (12.3)	11 (23.9)	9 (29.0)	4 (10.0)	7 (35.0)	3 (12.5)
5 to ≤10	2 (2.5)	0 (0.0)	1 (3.2)	6 (15.0)	3 (15.0)	3 (12.5)
>10	0 (0.0)	2 (4.3)	3 (9.7)	4 (10.0)	0 (0.0)	1 (4.2)
Injection-site swelling (cm)						
any	14 (17.3)	14 (30.4)	17 (54.8)	15 (37.5)	8 (40.0)	8 (33.3)
0 to ≤5	12 (14.8)	11 (23.9)	10 (32.3)	5 (12.5)	3 (15.0)	5 (20.8)
5 to ≤10	2 (2.5)	1 (2.2)	5 (16.1)	8 (20.0)	5 (25.0)	2 (8.3)
>10	0 (0.0)	2 (4.3)	2 (6.5)	2 (5.0)	0 (0.0)	1 (4.2)
Any Systemic AE[$]	16 (19.8)	7 (15.2)	9 (29.0)	12 (30.0)	5 (25.0)	9 (37.5)
Diarrhoea	2 (2.5)	1 (2.2)	2 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)
Malaise	0 (0.0)	1 (2.2)	2 (6.5)	1 (2.5)	0 (0.0)	0 (0.0)
Fever[#]	1 (1.2)	1 (2.2)	1 (3.2)	5 (12.5)	0 (0.0)	4 (16.7)
Nasopharyngitis	1 (1.2)	1 (2.2)	0 (0.0)	2 (5.0)	1 (5.0)	0 (0.0)

[#]Injection site AEs and fever were collected from Day1 through Day 5. [$] Systemic AEs were collected from Day 1 through Day 14. The size of injection-site erythema and swelling were measured by inch and then converted to the centimeter (cm). N: number of subjects in the vaccination group; n: number of subjects in the indicated category

6 years (up to 11 years after the primary vaccination). Administration of a second dose of PPSV23 resulted in increases of serotype-specific IgG concentrations and OPA titers for all serotypes and the elevated IgG and OPA levels in all revaccination subgroups were comparable to those in the primary vaccination group. Additionally and for majority of serotypes tested in the study, postvaccination IgG and OPA levels were comparable across all revaccinated subjects, regardless of the time interval since the primary vaccination. This finding indicates that revaccination with PPSV23 can elicit comparable immune responses to primary vaccination in adults aged 70 years and older regardless of time interval after primary vaccination when a second dose of PPSV23 is administered at least 5 years after the initial vaccination. Our study results are consistent with a recent publication from the Standing Committee on Vaccination (STIKO) in Germany which provided the scientific justification for the update of the pneumococcal vaccination recommendation for senior citizens.[13,20] In their analysis of previous studies assessing immunogenicity following revaccination with PPSV23, they showed that serotype-specific IgG levels measured 5–10 years after the second dose of PPSV23 were consistently higher or comparable to those measured 5–10 years after the initial dose of PPSV23, indicated that IgG levels following revaccination with PPSV23 persist for 5 years or more, at levels comparable to those observed following primary vaccination.

Safety analysis showed that the solicited injection-site AEs were higher in the revaccination subgroups at any time interval than in the primary vaccination group, but most injection-site AEs were mild to moderate in intensity. The higher incidences and intensity of injection-site AEs may be attributed to higher baseline antibody levels in the revaccination subgroups compared to those in the primary vaccination group.[19] The incidence of fever in the revaccination subgroups at the 7-year and the 9 to 11-year interval were higher than those at 5-year, 6-year and 8-year interval. Of 5 subjects who reported fever in the revaccination subgroups at the 7-year interval, 4 subjects were 77 to 78 years of age and developed fever on Day1 (on the same day of revaccination) or Day2 after revaccination with PPSV23. 1 subject aged 89 years old developed fever on Day 4 after revaccination with PPSV23. These findings indicate that there was no clear relation between the incidence of fever and age. Most reported cases of fever were below 38.5°C, transient and resolved within 4 days. Importantly, there was no difference in the intensity of injection-site and systemic AEs among the revaccination subgroups at any time intervals. No death was reported in the study and no subject discontinued from the study due to vaccine-related AE. As observed above, safety and tolerability profiles of revaccination with PPSV23 at interval of 5 to 11 years after the initial vaccination were acceptable. Considering the acceptable safety profiles and continued prevention of pneumococcal diseases in elderly adults, it may be beneficial to administer a second dose of PPSV23 as early as 5 years after the initial vaccination.

A potential limitation of this analysis is that original study was not designed to assess the immunogenicity and safety in the revaccination subgroups by time interval after the initial vaccination and the sample sizes of each revaccination subgroup by time interval were small, therefore, the small number of subjects limit the ability to make clear policy recommendations regarding the optimal time interval beyond the five-year interval for the second dose of PPSV23, and only subset of serotypes in the PPSV23 were evaluated for IgG concentrations and OPA titers.

Conclusion

The conclusions led by this post-hoc analysis are that a second dose of PPSV23 administered at least 5 years after the initial vaccination displayed the acceptable safety profiles

and elicited satisfactory immune responses in adults ≥70 years of age regardless of the time interval after the initial vaccination. This post-hoc analysis is valuable when considering the optimal timing for revaccination with PPSV23 in adults ≥70 years of age who have received their first vaccination at least 5 years before.

Materials and methods

Study design

This report is a pot-hoc analysis of immunogenicity and safety in a subset of subjects who received a second dose of PPSV23 in the original study which was conducted at 5 sites between November 2014 and May 2015. The original study was a non-randomized, multi-site, open label study to evaluate the safety and immunogenicity of a second dose of PPSV23 in the Japanese elderly.[12] A total of 242 subjects were enrolled in either primary vaccination group (81 subjects) or revaccination group (161 subjects) and subjects in both groups received a single dose of PPSV23 intramuscularly. Subject background such as age, gender and number and type of comorbidity (i.e., chronic heart disease, chronic lung disease, and diabetes mellitus) were matched between primary vaccination and revaccination group in order to eliminate the potentially confounding factors associated with safety and immunogenicity in the primary and revaccination with PPSV23.

Study objectives

In this analysis, no statistical significance test for the immunogenicity and safety were performed. The purpose of post-hoc analysis for immunogenicity was to show the serotype-specific IgG GMCs to 14 serotypes and serotype-specific OPA GMTs to 6 serotypes in the revaccination with PPSV23 at an interval of 5, 6, 7, 8 and 9 to 11 years after the initial vaccination. The safety and tolerability of revaccination with PPSV23 at an interval of 5, 6, 7, 8 and 9 to 11 years were summarized.

Study population

Japanese male and female between 70 and 89 of age were eligible for the study. Subjects who had no prior history of PPSV23 vaccination were assigned to the primary vaccination group and subjects who had a confirmed record of prior PPSV23 vaccination at least 5 years before study enrollment were assigned to the revaccination group. Subjects who had a stable underlying medical condition were included in the study. Subjects in both groups were excluded if they: had a history of pneumococcal conjugate vaccine; had an allergy or sensitivity to any of the components of the pneumococcal polysaccharide vaccine; were immunocompromised; were undergoing immunosuppressive therapy such as systemic corticosteroids; had a severe underlying medical condition; had recent receipt of immune globulin within 6 months before study enrollment; or had a coagulation disorder contraindicating intramuscular injection. The study was conducted in accordance with principles of Good Clinical Practice, approved by the Institutional Review Board of each participating site, and written informed consent was obtained from subject prior to study entry. This study is registered with ClinicalTrials.gov, number NCT02260882.

Vaccine descriptions

Study vaccines (Pneumovax®NP, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA) is a sterile, liquid product consisting of a mixture of purified capsular polysaccharides from *Streptococcus pneumoniae* types (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F). Study vaccine contains 25 μg of each polysaccharide type in isotonic saline solution. Study vaccine was provided as a single-dose glass vials containing of 0.5 mL of products and stored below 8°C.

Measures

Immunogenicity

A 7 mL blood sample was collected before and 4 weeks after vaccination with PPSV23 to assess antibody responses included in the study vaccine. Sera were separated and stored at −20°C. IgG antibody concentrations to 14 serotypes included in PPSV23 (serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F) were measured using pneumococcal electrochemiluminescence (Pn ECL) assay.[21] OPA was measured for 6 serotypes (3, 4, 6B, 14, 22F, and 23F) using multiplexed OPA (MOPA) assay.[22] The Pn ECL and OPA testing were performed at PPD Vaccines and Biologics Laboratory (Wayne, PA, USA) and at the University of Alabama (Birmingham, AL, USA), respectively.

Safety

All subjects were followed for safety for 14 days after vaccination with PPSV23. The subject was instructed to record oral temperatures and solicited injection-site AEs included redness (erythema), swelling and pain/tenderness from Day 1 to Day 5 and all adverse events from Day 1 through Day 14 on a vaccination report card. Severe AEs were collected throughout the study. Maximum oral temperature ≥ 37.5 °C was counted as fever in this analysis.

Statistical analysis

Immunogenicity

There were no immunogenicity hypotheses for this post-hoc analysis. All subjects who received a single dose of study vaccine and were adhered to the study procedures were included in the immunogenicity analysis. The IgG GMCs for 14 serotypes and OPA GMTs for 6 serotypes were calculated along with the 95% CIs by time interval after the initial vaccination. For each serotype, the individual IgG concentrations were natural log-transformed. The two-sided 95% CIs for mean IgG concentrations were calculated on the natural log scale and reference a t-distribution. Then the means and CIs were back transformed to obtain the corresponding point estimates and 95% CI s for IgG GMCs on the original scale by time interval after the initial vaccination. The same approach was used to estimate OPA GMTs and each GMFR.

Safety

There are no safety hypotheses for this post-hoc analysis. All subjects who received a single dose of study vaccine and had safety follow-up were included in the safety analysis. The frequencies and percentages of subjects who experienced adverse events in the primary and revaccination subgroups at time interval after the initial vaccination were summarized.

Disclosure of potential conflicts of interest

In conjunction with the external investigators, this study was designed, executed, and analyzed by the sponsor. The sponsor formally reviewed a penultimate draft. All co-authors approved the final version of the manuscript. KK received payment for lectures and manuscript preparation from MSD K.K. HK, SK, KT, TI, MS are employees of MSD K.K., Japan, a group of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. LM is employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Employees may hold stock and/or stock options in the company.

Acknowledgments

The authors would like to thank all the investigators and the participants for participating in this trial.

Funding

This study was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (sponsor).

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