mice. Altered pulmonary defense caused by prior influenza virus infection caused rapid bacterial growth in the lung, and bacteremia developed subsequently in these mice.

Previous reports suggest several possible mechanisms to explain the impaired host defense against pneumococcal pneumonia after influenza virus infection, such as the production of IL-10 [28], interferon-γ (IFN-γ) [29], and type 1 IFNs [30], and desensitization to bacterial Toll-like receptor ligands [31]. Shahangian et al. suggested that the production of type 1 IFNs in the lung triggered by prior influenza virus infection inhibits CXC chemokine production and subsequently decreases the pulmonary influx of polymorphonuclear (PMN) cells [30]. We found a marked influx of PMN cells into BAL fluid from mice immunized nasally with PspA/poly(I:C) or PBS/poly(I:C) after secondary pneumococcal pneumonia. A similar finding of the influx of granulocytes into BAL fluid has been shown in a murine model of secondary pneumococcal pneumonia [28]. In addition, King et al. recently reported a >1800-reduction in the growth of the PspA$^-$ mutant relative to that of the wild-type *S. pneumoniae* D39 strain in mice with prior influenza virus infection, which was highly significant compared with the growth of PspA$^-$ mutant in mice without prior influenza virus infection [32]. This finding suggests that PspA is a critical pathogenic factor in this murine model of secondary pneumonia.

Our previous study of a sublethal pneumonia model using the WU2 strain showed that intranasal immunization of mice with a high dose (2.5 μg) of PspA and 10 μg of a TLR agonist (Pam3CSK4, poly(I:C), lipopolysaccharide, or CpG1826) increased the level of PspA-specific IgG in blood and PspA-specific IgA in the airways [23]. Among these TLR agonists, poly(I:C) is a synthetic analog of dsRNA. Since Poly I:PolyC12 U (Ampligen®), a synthetic dsRNA compound, which can act as a mucosal adjuvant for influenza virus [33], is applicable for humans [34], we used poly(I:C) as a mucosal adjuvant for PspA in this study. Although a previous study employing a PspA DNA vaccine suggested that a balanced IgG1/IgG2a immune response to PspA might increase the complement deposition, and the protection against pneumococcal infections [35], our previous study demonstrated the effects of nasal immunization with PspA plus different TLR agonists on bacterial clearance from the airways were equivalent between the different TLR agonists despite the balance of IgG1/IgG2a immune responses to PspA [23].

An intranasal administration of a low dose of PspA and poly(I:C) induced a higher level of PspA-specific IgG in blood and a low level of PspA-specific IgG, but not IgA, in BAL fluid of mice. PspA-specific IgG induced in serum bound to the surface of the WU2 strain and caused the strong deposition of C3 on the WU2 strain. This nasal vaccine with a low dose of PspA caused a marked reduction of the bacterial growth in the lung (500–13,000-times lower), and inhibited bacteremia completely, and subsequently improved the survival rate of mice with secondary pneumonia. Furthermore, the productions of tumor necrosis factor (TNF)-α and macrophage inflammatory protein (MIP)-2α in serum of mice nasally immunized with PspA/poly(I:C) were completely suppressed at 72 h after secondary pneumonia, compared with those in sera of mice nasally immunized with PBS/poly(I:C) alone (data not shown). These data suggest a complete suppression of bacteremia subsequently inhibited the systemic inflammatory responses in mice nasally immunized with PspA/poly(I:C).

Although our recent study confirmed the role of PspA-specific IgA in bacterial clearance of the serotype 19F strain of EF3030, which was relatively avirulent and caused bacterial colonization in the airway [36], PspA-specific IgA seems to not be essential in a model of bacteremic pneumonia using a virulent serotype 3 strain of WU2 in mice. By contrast, the successful protection of mice from death by passive transfer of anti-PspA serum shown in this study suggests that PspA-specific IgG plays a pivotal role through binding to the bacterial surfaces and increasing C3 deposition on the bacterial surfaces in a fatal model of secondary pneumonia using the WU2 strain.

A recent study also reported that nasal immunization with 1.0 μg of PspA plus 4 μg of cholera toxin B subunit reduced the bacterial load of serotypes 2, 3, and 4 pneumococci in the lungs of mice with secondary pneumonia after influenza virus infection measured 24 h after pneumococcal challenge compared with control mice [32]. However, the magnitude of the reduction in the bacterial load in the lung by this intranasal PspA vaccine was only less than 100-fold, and no induction of PspA-specific antibodies or increased survival of mice with secondary pneumonia was observed.

In conclusion, intranasal vaccination with a low dose of PspA plus poly(I:C) induced a high level of PspA-specific IgG in serum but a low level of PspA-specific IgG in BAL fluid. PspA-specific IgG bound to invasive pneumococci and led to the deposition of C3 on this bacteria. Intranasal vaccination had a marked antibacterial effect in a fatal model of pneumococcal pneumonia after influenza virus infection. Our data suggest that intranasal vaccination with a low dose of PspA plus poly(I:C) is highly protective against secondary pneumococcal pneumonia, which is seen frequently in children and adults during pandemic influenza and epidemics of seasonal influenza.

Acknowledgments

We thank D.E. Briles, University of Alabama at Birmingham, for providing the pneumococcal strain WU2 and the recombinant plasmid pUAB055. We are also grateful to K. Ichida, M. Takahashi, and M. Tsujimoto, Laboratory Diagnostic Service Division, The Research Foundation of Microbial Diseases, Osaka University, for their technical assistance and comments on the histological material.

This work was supported by the Program for Promotion of Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation (NIBIO), and by the Biomedical Cluster Kansai project, which is promoted by the Regional Innovation Cluster Program and subsidized by the Japanese Government, and by Grants-in-Aid from the Ministry of Health, Labor and Welfare of Japan for "Mechanisms, epidemiology, prevention and control of acute respiratory infection".

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Vaccine 28 (2010) 7063–7069

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Effectiveness of pneumococcal polysaccharide vaccine against pneumonia and cost analysis for the elderly who receive seasonal influenza vaccine in Japan

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ARTICLE INFO

Article history:
Received 22 April 2010
Received in revised form 29 July 2010
Accepted 2 August 2010
Available online 17 August 2010

Keywords:
Pneumococcal polysaccharide vaccine
Influenza vaccine
Pneumonia
Cost analysis

ABSTRACT

To determine the clinical efficacy and cost-saving effect of pneumococcal polysaccharide vaccine (PPV) against community-acquired pneumonia (CAP), an open-label, randomized clinical trial was conducted involving 786 Japanese subjects older than 65 years of age receiving a routine influenza vaccine during the 2-year period. Study subjects were randomly assigned to either a PPV group ($n = 394$) or to a non-PPV group ($n = 392$). The incidence, admission and the medical cost for all-cause pneumonia were compared between these two groups. PPV vaccination significantly reduced the incidence of admission for all-cause pneumonia for subjects older than 75 years of age (41.5%, $P = 0.039$) and for those who had difficulty walking (62.7%, $P = 0.005$), but not for all study subjects older than 65 years of age ($P = 0.183$), for the 2-year period. The Kaplan–Meier survival curves for subjects who had difficulty walking free from all-cause pneumonia demonstrated a significant difference ($P = 0.0146$) between the two groups. PPV vaccination significantly reduced medical costs for all study subjects during the first year period ($P = 0.027$). Our present data demonstrated that PPV was effective for all-cause pneumonia for study subjects older than 75 years of age, although the effect was not significant for all study subjects older than 65 years of age.

1. Introduction

Streptococcus pneumoniae (*S. pneumoniae*) is a leading human pathogen causing a variety of diseases in children and adults such as otitis media, and invasive pneumococcal diseases (IPD), including sepsis, meningitis and bacteremic pneumonia. The rates of IPD are highest among children under 5 years of age, and among adults who are older than 65 years of age [1,2]. *S. pneumoniae* is the most common cause of community-acquired pneumonia (CAP) in adults [3,4]. The incidence of pneumococcal CAP is also high among the elderly [4–6].

The 23-valent pneumococcal polysaccharide vaccine (PPV) has proven to be protective against IPD in immunocompetent adults. However, information is lacking about its efficacy in adults with chronic illnesses [7–10]. Although PPV vaccination reportedly reduces the mortality and ICU admissions for pneumonia [11,12], the evidence of its efficacy against all-cause pneumonia remains inconclusive [7,9,13,14].

The importance of the cost-effectiveness of vaccines is becoming an increasingly important aspect of decision-making with regard to vaccine policy. Recently, it was reported that PPV is a cost-effective measure for prevention of invasive pneumococcal diseases (IPD) (less than $50,000 per life-year gained [LYG] or per quality-adjusted life-year gained [QALY]) [15–18]. These studies evaluated the cost-effectiveness of PPV only in the base-case analysis for overall IPD. Furthermore, Ament et al. have reported that PPV vaccination is assumed to be cost-effective for pneumococcal pneumonia as well as IPD [19]. However, these findings may not persuade policy makers in Japan because of the differences in the organizations and costs for health care when comparing U.S. or European countries with Japan.

As a result of insufficient evidence supporting the clinical efficacy and cost-effectiveness of PPV against all-cause pneumonia, PPV has not been included in the national immunization program in Japan. This results in a low coverage of PPV (approximately 7%) among Japanese older than 65 years of age. To address these issues, we designed an open-labeled, randomized clinical trial to determine whether PPV vaccination reduces the incidence rate and number of admissions for all-cause pneumonia among individuals older than 65 years of age in Japan who receive routine immunization with seasonal-influenza virus vaccine (IV). Additionally, we

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doi:10.1016/j.vaccine.2010.08.010

compared the medical costs for all-cause pneumonia for the study participants who received PPV with those of participants who did not receive PPV.

2. Materials and methods

2.1. Study design

During the 2-month period of October and November 2005, the present study enrolled 786 adults older than 65 years of age and who had received routine immunization against seasonal influenza. The subjects were randomly assigned to either the PPV group or the non-PPV group by choosing a sealed envelope that contained a card indicating one of the two groups, because we were unable to mobilize the staff needed for a blinded randomization of the participants during the 2-month period of enrollment. All participants received a trivalent, split-virion influenza vaccine (IV). The 2005/2006 vaccine contained A/New Caledonia/20/99H1N1, A/New York/55/04H3N2, and B/Shanghai/361/2002 (The Chemo-Sero-Therapeutic Research Institute, Kumamoto, Japan) and the 2006/2007 vaccine contained A/New Caledonia/20/99H1N1, A/Hiroshima/52/05H3N2, and B/Malaysia/2506/04 (The Chemo-Sero-Therapeutic Research Institute). The participants in the PPV group were immunized with 0.5 ml of 23-valent PPV (Pneumovax, Banyu, Japan) with a 1-month interval after receipt of their seasonal influenza vaccine in 2005. The participants in the non-PPV group received only seasonal influenza vaccine in 2005. The participants in both the PPV and the non-PPV groups received only seasonal influenza vaccine in 2006. Demographic data were obtained from each participant at the time of enrollment. The present study was approved by the institutional review boards for the Nagasaki Kawatana Medical Center (NKMC) and the Faculty of Medicine, Nagasaki University, Japan.

2.2. Study population

The study population consisted of individuals routinely followed by pulmonary physicians (KK, RK, TY, KK, and YH) at the Department of Respiratory Medicine of NKMC and by general physicians at twelve private clinics in Kawatana, Hasami and Higashisonogi townships, Nagasaki Prefecture. Individuals who were bed-ridden or had immunocompromised conditions such as active malignant diseases, or anatomical or functional asplenia and who had previously received PPV were excluded from the study.

After written informed consent, 786 individuals older than 65 years of age who received routine immunization by IV between October and November 2005, were assigned to either the PPV ($n = 394$) or to the non-PPV group ($n = 392$) (Fig. 1). Lost to follow-up during the 2-year period were 3 and 5 subjects from the PPV and non-PPV groups, respectively. As a result, 391 subjects in the PPV group and 387 subjects in the non-PPV group completed the entire study. These subjects were further classified into six subgroups according to their underlying diseases, age or physical conditions (Table 1). A subgroup of chronic lung diseases involved subjects with bronchial asthma, chronic obstructive pulmonary diseases (COPD), sequelae of pulmonary tuberculosis, or pneumoconiosis. A subgroup for subjects who experienced a prior episode of pneumonia was defined as subjects who experienced pneumonia during the last 5 years. There was a subgroup for subjects who had difficulty walking and had to use a stick or a wheel-chair. Of the 128 subjects in this subgroup, 105 (82.0%) were older than 75 years of age, and had comorbid illnesses, such as cerebrovascular diseases, congestive heart failure, COPD, and dementia.

Since research of the literature indicated the substantial probability of a false positive finding when multiple subgroup analyses

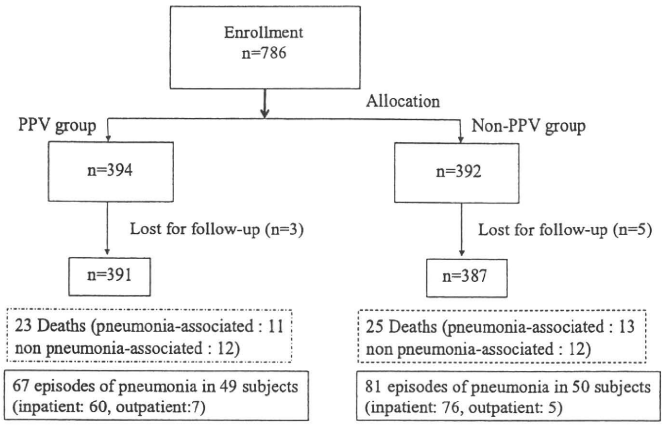

Fig. 1. Flow diagram of study subjects.

are performed [20], we carefully planned, reported and interpreted these results according to the guidelines for reporting subgroup analyses [21].

2.3. Outcome measures

All participants were examined for their underlying diseases either at a private clinic or at the NKMC once or twice per month by the study investigators. Patients were also asked to visit either their clinic or the NKMC for examination by a study investigator, if they developed a fever or respiratory symptoms during the 2-year follow-up period. The primary endpoints were all-cause pneumonia and admissions due to all-cause pneumonia. The secondary endpoint was the medical cost of all-cause pneumonia. The time to the first episode of all-cause pneumonia after the enrollment in this study was recorded. A pneumonia diagnosis was based on clinical symptoms (cough, sputum or fever), increased white blood cell counts or serum C-reactive protein, and the appearance of an infiltration on a chest radiograph or chest computed tomography at the hospital or the clinics of the study investigator [4].

The medical cost for each study participant of the PPV group was defined as the cost for both PPV and IV vaccinations plus cost for medical care of all-cause pneumonia during the study period. The medical cost for each participant of the non-PPV group was defined as the IV vaccination fee plus medical care for all-cause pneumonia during the study period. An indirect cost from loss of patient productivity, which mostly consisted of missed work was disregarded because the study population was older than 65 years of age.

2.4. Data collection

After enrollment, the study participants were followed by the study coordinators (TK, MM) by means of telephone interview on a monthly basis for recent episode of pneumonia. When the study coordinators identified an episode of pneumonia-like illness for the study participant, they confirmed with the responsible physician if the study participant had received a radiological diagnosis of pneumonia, and had received medical care for pneumonia at the private clinics or NKMC. After confirmation of a pneumonia episode for the study participant, the study coordinator collected the receipt for medical care of this pneumonia episode at the inpatient or outpatient clinic from the study participant, and calculated the medical cost for a single episode of pneumonia according to the detailed invoice and the reimbursement system for each individual.

Table 1
Comparison of demographic features of enrolled subjects by vaccine group.

	PPV group (n = 391)	Non-PPV group (n = 387)	P-value
Age; mean (SD)	78.5 (7.3)	77.7 (7.2)	0.133
Male sex (n = 274)	149 (38.1)	125 (32.3)	0.133
Categories (n)	No. of subjects (%)		
Older than 75 years (n = 511)	264 (67.5)	247 (63.8)	0.291
Chronic heart diseases and hypertension (n = 503)	261 (66.8)	242 (62.5)	0.767
Chronic lung diseases (n = 130)	73 (18.5)	57 (14.5)	0.150
Chronic renal diseases (n = 102)	59 (15.1)	43 (9.1)	0.164
Prior episode of pneumonia (n = 50)	25 (6.4)	25 (6.3)	0.464
Difficulty walking (n = 128)	63 (16.1)	65 (16.8)	0.822

2.5. Statistical analysis

An interim target sample size of 658 was chosen to ensure that there would be at least an 80% chance to detect a difference of 0.05 (0.06 vs. 0.1) episodes per person per year, with a one-sided alpha level of 0.05, in the incidence of all-cause pneumonia between the PPV group and the non-PPV group. The incidence of all-cause pneumonia and admission due to all-cause pneumonia, and the total medical costs including vaccine for all-cause pneumonia for several prespecified subgroups were compared using a chi-square test. A Kaplan–Meier estimator was used to calculate the survival curve for subjects who did not acquire all-cause pneumonia during a 2-year period. A Cox's proportional hazard model for adjusting age and gender was also used to determine the effect of PPV on the incidence rate of all-cause pneumonia in the subgroups during the first year period as well as for the entire 2-year period. The effect of PPV on medical cost was estimated using a linear regression model, whereby the medical cost regressed on PPV, age and gender [22–25]. Namely, the estimation equation was as follows; $(\text{medical cost})_i = \alpha + \beta(\text{PPV})_i + \gamma(\text{age})_i + \delta(\text{gender})_i + \varepsilon_i$; where i indicates a study participant. $(\text{PPV})_i$ indicates 0 for the non-PPV group and 1 for the PPV group. The effect of PPV on medical cost was estimated as the estimator of β. All costs were calculated in US dollars (USD) and adjusted for inflation using the 2007 consumer price index and exchange rates (1 USD = 115 yen). The costs for a single dose of PPV and two doses of IV were 61 USD and 73 USD, respectively. Data was considered to be statistically significant, when the P values were less than 0.05.

3. Results

The mean age ± SD for the PPV group was 78.5 ± 7.3 and 38% were male. For the non-PPV group, the mean age ± SD was 77.7 ± 7.2 and 32.3% were male. The numbers of subjects within each subgroup is summarized for the two groups in Table 1. No significant differences were found between the two groups with respect to the number of subjects older than 75 years of age, with chronic heart diseases and hypertension, with chronic lung diseases, with chronic renal diseases, with a prior episode of pneumonia, or with difficulty walking. No significant difference was found between the two groups with respect to the number of pneumonia-associated deaths (11 for the PPV group and 13 for the non-PPV group; P = 0.660) nor for non pneumonia-associated deaths (12 for the PPV group and 12 for the non-PPV group; P = 0.852) during the 2-year period (Fig. 1). The PPV group recorded 67 episodes of pneumonia, and 81 were identified in the non-PPV group. Treatment for pneumonia was performed at the inpatient clinic for 60 episodes and at the outpatient clinic for 7 episodes for the PPV group, while the non-PPV group sought treatment for pneumonia at the inpatient clinic for 76 episodes and at the outpatient clinic for 5 episodes.

No significant difference was found in the incidence of all-cause pneumonia between all subjects in the PPV group (0.086 per person year) and the non-PPV group (0.105 per person year) during the 2-year study period (P = 0.221, Table 2). By contrast, the incidence of all-cause pneumonia among subjects older than 75 years of age for the PPV group (0.068 per person year) was significantly lower than it was for the non-PPV group (0.134 per person year) during the first year of the study (P = 0.017), but not for the entire 2-year period (P = 0.072). This also was true for subjects with chronic lung diseases, who demonstrated a significant reduction in the incidence for the PPV group (0.096 per person year), compared with the non-PPV group during the first year (P = 0.035), but not for the entire 2-year period (P = 0.233). Furthermore, for subjects who had difficulty walking, the incidence of all-cause pneumonia for the PPV group (0.135 per person year) was significantly lower (P = 0.0006) than it was for the non-PPV group (0.331 per person year) for the 2-year period while no significant differences were found between the two groups among the subjects with chronic heart diseases and hypertension, chronic renal diseases, and with a prior episode of pneumonia. While no significant differences were found in the incidence of admissions for all-cause pneumonia between the two groups (Table 3), significant differences were found between the two groups for subjects older than 75 years of age (P = 0.039 for the 2-year period) and for the subjects who had difficulty walking (P = 0.005 for the 2-year period).

The mean cost of 12 subjects for medical care of pneumonia at outpatient clinics was 310 USD per episode. By contrast, the mean cost of 137 subjects for medical care of pneumonia at the inpatient clinics was higher (9195 USD per episode). For all subjects, a significant reduction in the medical cost was found in the PPV group, compared with the non-PPV group during the first year (P = 0.027, Table 4), but not for the 2-year period (P = 0.111). Significant reductions in the medical cost were also found for subjects older than 75 years of age (P = 0.018) and for subjects with chronic lung diseases (P = 0.017) during the first year. The reductions in medical cost averaged 1079 USD for subjects older than 75 years of age and 2672 USD for subjects with chronic lung diseases. It is noteworthy that a significant reduction in medical cost was found for subjects who had difficulty walking (P = 0.004), and this reduction averaged 2467 USD for the 2-year period.

There was a significant association recorded between the receipt of PPV and a low probability of pneumonia was found for the subjects who had difficulty walking for both the first year (P = 0.037) and the entire 2-year period (P = 0.006) (Table 5). However, none of the multivariate analyses demonstrated a significant association between any variables for all study subjects, and the probability of all-cause pneumonia in either the first year or the 2-year period. Similarly, the Kaplan–Meier survival curves for the subjects with difficulty walking who were free from all-cause pneumonia demonstrated a significant difference between the two groups (P = 0.0146) (Fig. 2), while no significant difference was found in the Kaplan–Meier survival curves for study subjects older than either 65 (P = 0.750) or 75 years of age (P = 0.199) who were free

Table 2
Incidences of all-cause pneumonia by vaccine group during a period of 2 years after enrollment among subjects with different categories (age and gender adjusted).

Categories (*n*)	Period	Incidence of all-cause pneumonia (per person years)		% Reduction in incidence of all-cause pneumonia (95% CI)	*P*-value
		PPV group	Non-PP V group		
All subjects (*n* = 778)		*n* = 391	*n* = 387		
	First year	25 (0.064)	37 (0.096)	41.70 (−6.9–69.2)	0.082
	Two years	67 (0.086)	81 (0.105)	24.75 (−18.5–52.8)	0.221
Older than 75 years old (*n* = 511)		*n* = 264	*n* = 247		
	First year	18 (0.068)	33 (0.134)	59.08 (14.05–82.40)	0.017
	Two years	51 (0.097)	69 (0.140)	36.58 (−4.09–61.97)	0.072
Chronic heart diseases and hypertension (*n* = 503)		*n* = 261	*n* = 242		
	First year	18 (0.069)	12 (0.050)	−38.26 (−230.88–43.24)	0.472
	Two years	41 (0.079)	34 (0.069)	−8.45 (−107.30–44.77)	0.810
Chronic lung diseases (*n* = 130)		*n* = 73	*n* = 57		
	First year	7 (0.096)	15 (0.263)	60.60 (6.32–82.63)	0.035
	Two years	25 (0.171)	33 (0.289)	31.59 (−28.26–62.23)	0.233
Chronic renal diseases (*n* = 102)		*n* = 59	*n* = 43		
	First year	4 (0.068)	5 (0.116)	55.33 (−108.74–97.13)	0.325
	Two years	14 (0.119)	10 (0.116)	17.64 (−281.91–95.97)	0.822
Prior episode of pneumonia (*n* = 50)		*n* = 25	*n* = 25		
	First year	7 (0.280)	11 (0.440)	26.33 (−94.17–72.93)	0.539
	Two years	21 (0.420)	21 (0.420)	−20.142 (−136.03–39.12)	0.596
Difficulty walking (*n* = 128)		*n* = 63	*n* = 65		
	First year	8 (0.127)	24 (0.369)	67.05 (17.30–88.37)	0.017
	Two years	17 (0.135)	43 (0.331)	60.91 (23.46–80.78)	0.006

from all-cause pneumonia between the two groups (data not shown).

4. Discussion

In the present study, PPV vaccination, in addition to routine IV vaccination, did not significantly reduce the incidence of all-cause pneumonia for all study subjects older than 65 years of age. In contrast, PPV vaccination significantly reduced the incidence of all-cause pneumonia compared with routine IV vaccination alone, by 59.1% for subjects older than 75 years, by 60.6% for subjects with chronic lung diseases, and by 60.9% for subjects who had difficulty walking for the first year of the study period. Furthermore, for the 2-year period, PPV vaccination in addition to routine IV vaccination resulted in significant reductions in admissions for all-cause pneumonia: by 41.5% for subjects older than 75 years of age and by 62.7% for subjects who had difficulty walking.

A higher reduction in the incidence of all-cause pneumonia brought about by PPV vaccination for subjects older than 75 years of age compared with all study subjects could be explained, in part, by a higher incidence of pneumococcal pneumonia for these subjects [4,26]. The highest reduction in the incidence of all-cause pneumonia brought about by PPV vaccination in subjects who had difficulty walking could be explained by the fact that more than 80% of these subjects were older than 75 years of age and these subjects had comorbid illnesses, such as cerebrovascular diseases and COPD, which are known risk factors for pneumococcal infection [27–29]. Previous studies also demonstrated the role of silent aspiration in the development of CAP in the elderly [30], and a high incidence of pneumonia has been found in the elderly with basal ganglia infarction [31]. In the present study, two different analy-

Table 3
Incidences of admission due to all-cause pneumonia by vaccine group during 2 years after enrollment among subjects with different categories (age and gender adjusted).

Categories (*n*)	Period	Incidence of admission due to all-cause pneumonia (per person years)		% Reduction in incidence of admission due to all-cause pneumonia (95% CI)	*P*-value
		PP V group	Non-PP V group		
All subjects (*n* = 778)		*n* = 391	*n* = 387		
	First year	25 (0.064)	35 (0.090)	38.17 (−13.12–67.29)	0.120
	Two years	60 (0.077)	76 (0.098)	27.33 (−16.32–55.79)	0.183
Older than 75 years old (*n* = 511)		*n* = 264	*n* = 247		
	First year	18 (0.068)	32 (0.130)	57.25 (11.49–81.12)	0.021
	Two years	46 (0.087)	67 (0.136)	41.52 (2.66–65.48)	0.039
Chronic heart diseases and hypertension (*n* = 503)		*n* = 261	*n* = 242		
	First year	18 (0.069)	11 (0.045)	−49.98 (−256.91–38.15)	0.366
	Two years	36 (0.069)	32 (0.066)	0.67 (−95.08–51.03)	0.985
Chronic lung diseases (*n* = 130)		*n* = 73	*n* = 57		
	First year	7 (0.096)	14 (0.246)	58.52 (−0.59–82.24)	0.052
	Two years	22 (0.151)	31 (0.272)	33.53 (−27.14–63.55)	0.180
Chronic renal diseases (*n* = 102)		*n* = 59	*n* = 43		
	First year	4 (0.068)	5 (0.116)	55.33 (−108.74–97.13)	0.325
	Two years	14 (0.119)	10 (0.116)	17.64 (−281.91–95.79)	0.822
Prior episode of pneumonia (*n* = 50)		*n* = 25	*n* = 25		
	First year	7 (0.280)	11 (0.440)	26.32 (−94.17–72.93)	0.539
	Two years	15 (0.300)	21 (0.420)	17.28 (−89.19–64.59)	0.570
Difficulty walking (*n* = 128)		*n* = 63	*n* = 65		
	First year	8 (0.127)	23 (0.354)	65.09 (14.15–87.17)	0.021
	Two years	16 (0.127)	42 (0.323)	62.74 (25.71–82.14)	0.005

Table 4
The total medical costs including vaccine for all-cause pneumonia by vaccine group during 2 years after enrollment among subjects with different categories (age and gender adjusted).

Categories (*n*)	Period	Total medical cost (mean, US$)		Reduction of medical cost due to all-cause pneumonia (US$) (95% CI)	*P*-value
		PPV group	Non-PPV group		
All subjects (*n* = 778)		*n* = 391	*n* = 387		
	First year	499	1225	661 (17–1304)	0.027
	Two years	1273	1978	320 (−113–753)	0.111
Older than 75 years old (*n* = 511)		*n* = 264	*n* = 247		
	First year	597	1741	1079 (136–2022)	0.018
	Two years	1667	2824	546 (−90–1182)	0.075
Chronic heart diseases and hypertension (*n* = 503)		*n* = 261	*n* = 242		
	First year	542	383	−224 (−818–370)	0.600
	Two years	1070	1094	−20 (−482–441)	0.959
Chronic lung diseases (*n* = 130)		*n* = 73	*n* = 57		
	First year	784	3522	2672 (461–4884)	0.017
	Two years	2690	5024	1135 (−316–2586)	0.117
Chronic renal diseases (*n* = 102)		*n* = 59	*n* = 43		
	First year	584	1292	640 (−806–2087)	0.341
	Two years	2100	1957	−104 (−1319–1111)	0.908
Prior episode of pneumonia (*n* = 50)		*n* = 25	*n* = 25		
	First year	1448	5996	4483 (−539–9506)	0.083
	Two years	2936	7745	2372 (−166–4910)	0.070
Difficulty walking (*n* = 128)		*n* = 63	*n* = 65		
	First year	1290	5387	4032 (849–7215)	0.013
	Two years	2193	7193	2467 (798–4137)	0.004

Table 5
Association of the receipt of PPV and the probability of all-cause pneumonia during the first one and two years (age and gender adjusted).

Period	Categories	All-cause pneumonia	
		Hazard ratio (95% CI)	*P*-value
First year	All subjects	0.73 (0.44–1.23)	0.251
	Age older than 75	0.55 (0.30–1.01)	0.053
	Chronic heart diseases and hypertension	1.58 (0.73–3.43)	0.247
	Chronic lung diseases	0.51 (0.21–1.19)	0.12
	Chronic renal diseases	0.56 (0.137–2.28)	0.417
	Prior episode of pneumonia	1.64 (0.63–4.21)	0.303
	Difficulty walking	0.41 (0.17–0.95)	0.037
Two years	All subjects	0.82 (0.55–1.23)	0.348
	Age older than 75	0.67 (0.42–1.06)	0.085
	Chronic heart diseases and hypertension	1.15 (0.64–2.05)	0.644
	Chronic lung diseases	0.79 (0.41–1.54)	0.501
	Chronic renal diseases	0.93 (0.29–2.88)	0.895
	Prior episode of pneumonia	1.51 (0.68–3.30)	0.303
	Difficulty walking	0.38 (0.19–0.76)	0.006

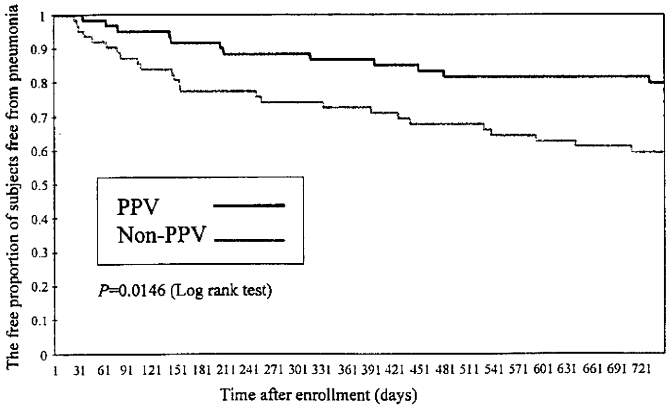

Fig. 2. Kaplan–Meier survival curve for study subjects who had difficulty walking showing the proportion of study subjects free from all-cause pneumonia between the PPV group (black line) and the non-PPV group (gray line) during the follow-up period. A significant difference in the proportion of study subjects who were free-from all-cause pneumonia was found between the two groups ($P = 0.0146$).

ses using the estimated results of Cox's proportional hazard model and the Kaplan–Meier survival curve similarly supported the significant protective effect of PPV vaccination for all-cause pneumonia in subjects who had difficulty walking.

On the other hand, the reason the effects of PPV vaccination were not found in other subgroups, such as chronic heart diseases and hypertension, chronic renal diseases and prior episode of pneumonia, may be explained, in part, by a low incidence in all-cause pneumonia for the subjects affected by such conditions in our patient sample.

The effect of PPV vaccination in the prevention of all-cause pneumonia during the first year period, but not for the 2-year period, for subjects older than 75 years of age and for those with chronic lung disease, may be explained by the kinetics of serotype-specific IgG determined by the third generation ELISA in the sera of subjects who received PPV vaccination [32]. The serum levels of serotype-specific IgG peaked at 2 months after PPV vaccination and they declined at 6 months after vaccination for most serotypes. Our previous study also showed that PPV had an effect on infectious acute exacerbation was found during the first year after vaccination, and was associated with a serotype-specific immune response

in the sera of patients with chronic lung diseases who received PPV vaccination [33].

Significant reductions in admissions for all-cause pneumonia were found following PPV vaccination, in addition to routine IV vaccination in subjects older than 75 years of age and in subjects who had difficulty walking during the 2-year period. Our data on the effects of PPV vaccination for hospital admissions for all-cause pneumonia are in agreement with the previous reports from a large cohort study of subjects older than 65 years of age in Sweden [34], and in a prospective study of the elderly in Japan [35]. A double- blind, randomized, controlled study has recently reported the efficacy of PPV in preventing pneumococcal pneumonia and reducing the mortality for pneumococcal pneumonia in nursing home residents in Japan [36]. Approximately 90% of the participants in this study were found to be older than 75 years of age, and this study also demonstrated a significant reduction in the incidence of all-cause pneumonia by PPV among the study subjects.

Although a previous study reported the cost-effectiveness of PPV for preventing pneumococcal pneumonia in five European countries, their results were based on the estimated incidence of pneumococcal pneumonia and on the estimated medical costs for vaccination and for treatment after admissions in each country [19]. In this regard, it is noteworthy that a significant reduction in direct medical costs (approximately 660 USD) for pneumonia was found in study subjects older than 65 years of age who received routine influenza vaccination during the first year following the PPV vaccinations in the present study. To our knowledge, this is the first report of the cost-saving effect of PPV for all-cause pneumonia among subjects in a randomized-controlled study. Significant reductions in higher medical costs for all-cause pneumonia among study subjects older than 75 years of age, those who had difficulty walking, and study subjects with chronic pulmonary diseases, were associated with a reduced incidence of hospital admissions for all-cause pneumonia, since the cost for one episode of hospital admission for all-cause pneumonia in the present study was more than 9000 USD. A high-risk population for all-cause pneumonia, such as subjects who had difficulty walking and subjects with chronic pulmonary diseases, are likely to have a higher reduction in medical costs for pneumonia.

Since no attempt was made to blind the clinical assessors to the vaccine allocation in the present study, the possibility of bias in the clinical assessments obtained by the investigators cannot be dismissed, and this would be one limitation. Another limitation is that the preventive effects of PPV for pneumococcal pneumonia were not evaluated in the present study, because the microbiological examinations were not routinely performed for all of pneumonia cases particularly in the private clinics.

In conclusion, during the 2-year period of the present study in Japan, PPV vaccination was effective in reducing the incidence of admission for all-cause pneumonia for subjects who were older than 75 years of age, although no significant effect was found for all-cause pneumonia in all study subjects older than 65 years of age. A cost-saving effect of PPV was also found for all-cause pneumonia in all study subjects during the first year of the present study. Our present data suggest a recommendation of PPV in combination with influenza vaccine for the people who are older than 75 years of age in Japan.

Acknowledgments

We are grateful to Dr. F. Konings, International Vaccine Institute, Seoul, Korea, for his critical review of this manuscript and M. Maekawa and K. Terumoto for their study coordination and collecting the information concerning the information medical costs of pneumonia. We are also grateful to the members of Medical Association of Higashisonogi district, Nagasaki Prefecture; Dr. T. Beppu, Dr. H. Kanazawa, Dr. H. Kohno, Dr. J. Matsuo, Dr. M. Motokawa, Dr. N. Nonaka, Dr. N. Okabe, Dr. F. Tamagawa, Dr. S. Tabuchi, Dr. N. Yamamoto and Dr. T. Yamazumi. This study was supported by a research grant "Studies on preventable vaccines for varicella, mumps, and pneumococcal pneumonia and other diseases" from the Ministry of Health, Labor and Welfare, Japan.

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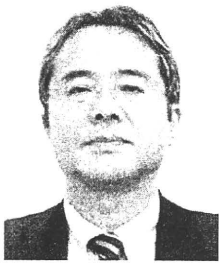
肺炎球菌ワクチンの複数回接種は必要か？

——2回接種の認可で十分かを検証する

Are 3 or more doses of pneumococcal polysaccharide vaccine required?



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◎23価肺炎球菌莢膜ポリサッカライドワクチン(PPV23)の再接種が，わが国においても2009年10月に承認された．本ワクチンの効果が5年間程度とされることから，高齢化社会を迎えたわが国においても今後のPPV23複数回接種についての議論の余地がある．

Key word：23価肺炎球菌ワクチン，複数回接種，安全性，免疫原性

23価肺炎球菌莢膜ポリサッカライドワクチン(PPV23)は，わが国において1988年に薬事承認された．この際に，再接種・追加接種をしてはならない旨が添付文書に記載された．本ワクチンが承認販売されている38カ国中，再接種が承認されていないのは日本だけであったが，この問題が2009年10月18日にやっと解決された．本稿ではPPV23の再接種承認に至った経緯，今後の複数回接種の必要性について検証する．

わが国におけるPPV23の位置づけ

肺炎球菌はもっとも重要な呼吸器病原性菌である．本菌はグラム陽性双球菌で多糖体(ポリサッカライド)からなる莢膜に覆われており，この莢膜ポリサッカライド(CPS)には，すくなくとも93の莢膜血清型が存在する．肺炎球菌感染症の病型の主体は，菌血症を伴う肺炎，髄膜炎などの侵襲性肺炎球菌性感染症(invasive pneumococcal diseases：IPD)と菌血症を伴わない肺炎(non-bacteremic pneumonia)であり，成人における肺炎球菌感染症の大半は後者である．この肺炎球菌感染症に対する感染防御において，その中心的役割を果たしているのが血清型特異的な抗CPS IgGによる補体依存的オプソニン活性である．PPV23は成人において血清型特異的液性免疫を誘導し，肺炎球菌感染症を予防する．

65歳以上の高齢者に対するPPV23の定期接種化を実現しているアメリカではその接種率が58%に達しているのに対し(Dr. Nourti私信，米国CDC)，わが国における同年齢層の接種率はいまだ7.8%と低い．本ワクチンがこれまでにわが国で普及しなかった理由として，①わが国における肺炎球菌感染症の疫学情報が不十分であること，②本感染症の主体を占める菌血症を伴わない肺炎に対する臨床効果のエビデンスがなかったこと，③本ワクチンに対する公費補助がなく，任意接種であったこと，などがあげられる．

再接種承認の経緯

2002年以降，わが国においてPPV23の高齢者に対する接種率が徐々に増加するにつれて，臨床現場では本ワクチンの再接種承認を求める声が高まってきた．すなわち，本ワクチンの初回接種による臨床効果の持続期間が約5年間とされている

表 1　肺炎球菌ワクチン再接種に関するアンケート調査

質問事項		人数(%)
所属施設における肺炎球菌ワクチンの接種	総対象者数：385 はいと回答した数 いいえ，あるいは無回答の数	 290(75.3) 95(24.7)
再接種禁忌が理由で初回接種を差し控えたか	対象者数：290 はいと回答した数 いいえ，あるいは無回答の数	 144(49.7) 146(50.3)
再接種を実施したか	対象者数：290 はいと回答した数 いいえ，あるいは無回答の数	 46(15.9) 244(84.1)
再接種承認が必要と思うか	対象者数：290 はいと回答した数 いいえ，あるいは無回答の数	 252(86.9) 38(13.1)

ことから，再接種を希望する高齢者(とくに慢性呼吸器疾患患者)が増加したのであった．

このような背景から PPV23 再接種の問題を解決すべく，2008 年から厚生労働省班会議“ワクチンの有効性向上のためのエビデンスおよび方策に関する研究”(班長：神谷　齊)による，わが国における，①肺炎球菌ワクチン再接種アンケート調査の実施[1]，②再接種の安全性・免疫原性に関する医師主導の臨床研究が開始された．2009 年 8 月には「日本感染症学会肺炎球菌ワクチン再接種問題検討委員会」名で“肺炎球菌ワクチン再接種に関するガイドライン”を日本感染症学会ホームページ上で公表した[2]．2009 年 9 月には，このガイドラインと③肺炎球菌ワクチン再接種問題検討委員会からの国内 3 学会の連名による厚生労働大臣への要望書を提出した．

これらの一連の問題解決に向けたアプローチから，厚生労働省は 2009 年 10 月 18 日に本ワクチンの再接種の承認を決定した．改訂された添付文書には，本剤の再接種を行う場合には再接種の必要性を慎重に考慮したうえで，前回接種から十分な間隔を確保して行うこととされている．

わが国における再接種のエビデンス

1. 再接種の実態と安全性

著者らは 2008 年度に日本呼吸器学会，日本感染症学会の評議員(代議員)以上に対し，肺炎球菌ワクチン再接種アンケート調査を実施した(表 1)[1]．その結果，調査対象者の医師 290 名のうち 86.9%が再接種は必要と認識しており，その 15.9%が再接種を実施した経験があった[1]．また，再接種が禁忌であるという理由から，初回接種を控える経験をした医師が約半数に及んでいたことも判明した．この事実は，前述したわが国における PPV23 ワクチンの普及に影響していたと考えられる．

一方，再接種を実施した調査対象者 46 名のうち 4 名から再接種に伴う副反応の報告があった．その内訳は，注射部位の局所的腫脹が 2 例，発疹，筋肉痛，倦怠感は各 1 例であった．1 例では 10 cm 以上の腫脹も経験されていたが，アナフィラキシーなど重篤な副反応の報告はなかった．

さらに，前述の国立病院機構東京病院で PPV23 の初回接種後 5〜6 年が経過した慢性肺疾患患者 50 症例(平均 76.4 歳)を対象として実施した“再接種の安全性・免疫原性に関する医師主導の臨床研究”(2009 年 8〜11 月実施)において，12%に接種後 1 週間以内の一過性の発熱，8〜65%に局所の腫脹・発赤が認められた[3]．しかし，すべての症状・所見は無治療で，再接種 6 日以内にすべて消失した．また，アナフィラキシーショックを含む重篤な副反応は認められなかった．

2. 再接種の免疫原性

前述の臨床研究における慢性肺疾患患者 40 例の血清中の主要 4 血清型に対する特異 IgG 抗体濃度(再接種前，1 カ月後)は，血清型 6B では(1.41，2.57 μg/ml)，血清型 14 では(4.22，7.32 μg/ml)，血清型 19F は(2.94，5.67 μg/ml)，血清型 23F は(1.45，2.95 μg/ml)であった[3]．PPV23 の

再接種1カ月後には，接種前に比較して有意に上昇していた．また，初回接種時と再接種時の接種前後の抗体濃度の増加比を比較したところ，再接種時の特異IgG抗体応答の低下は初回接種時の3～36％にとどまることが示された．PPV23に含まれるCPSはT細胞非依存性抗原であることから，再接種時のブースター効果が期待できない．しかし，今回の慢性肺疾患を対象とした臨床研究から，PPV23の再接種により初回接種にほぼ匹敵する特異IgG抗体産生が期待できることが判明した[4]．

PPV23の複数回接種

わが国においても，PPV23再接種による海外の成績と同等の安全性と免疫原性に関する成績が得られた．しかし，国内外を通してPPV23の再接種による臨床効果のエビデンスは，いまだないのが現状である．このためアメリカACIPは，65歳以上の免疫能が正常で肺炎球菌ワクチン接種後5年以上経過し，かつ前回接種が65歳未満であった場合には再接種を推奨しているものの，それ以後の複数回接種については言及していない[5]．

一方，肺炎球菌感染症が高頻度なアラスカ原住民においては，55歳以上の成人に対し6年ごとのPPV23の接種が推奨されており[6]，イギリスでも無脾症あるいは脾機能不全，慢性腎疾患患者では5年ごとの再接種が推奨されている[7]．また，ドイツ，フランス，オーストリア，スイスなども，ハイリスクの成人に対する複数回接種が承認されている．これらの国々では複数回接種の安全性と免疫原性より推定されるワクチン効果から，ハイリスク者の複数回接種を決定したと考えられる．わが国における平均寿命は2007年時点で，男性79.00歳，女性85.81歳であり，65歳の時点からは男性で14年，女性で20年の免疫原性の維持が必要となる．初回接種による血清特異抗体の維持期間は5年間程度とされるが，血清型や宿主によっては3年未満の場合もある[8]．さらに，再接種による血清特異抗体の維持期間の検討はいまだなく，わが国の高齢者において一体何回のPPV23接種が必要かを算定することは困難である．しかし理論的には，わが国の65歳以上の高齢者においてもPPV23の複数回接種は必要である．また，その安全性，免疫原性が確認されれば，複数回接種の承認も可能と考えられる．

わが国におけるPPV23の肺炎予防効果のエビデンス

これまでに蓄積された多くの肺炎球菌ワクチンの臨床試験において，免疫不全のない高齢者における菌血症を伴う肺炎，髄膜炎などの侵襲性肺炎球菌性感染症に対する予防効果が報告されているものの，すべての原因による肺炎の予防効果は明らかになっていない[9]．しかし，これまでに肺炎球菌ワクチンが成人肺炎の重症度，死亡リスクを低下させる効果が報告されており，成人の肺炎に対しては発症予防より重症化阻止ワクチンとしての意義があると考えられる[10-11]．

最近になってMaruyamaらは，わが国における1,006名の高齢者介護施設入居者（ほぼ100％がインフルエンザワクチン接種を受け，平均年齢約85歳）を対象としたPPV23の臨床効果に関する二重盲検無作為コントロール試験を実施し，世界ではじめてとなる肺炎球菌性肺炎に対する発症予防効果，肺炎球菌性肺炎による死亡数の減少効果を明らかにした[12]．PPV23接種により，すべての肺炎および肺炎球菌肺炎の頻度がそれぞれ44.8％，63.8％減少した．また，肺炎球菌性肺炎による死亡はプラセボ群で35.1％（13/37），PPV23接種群で0％（0/14）であり，両群間に有意差を認めた（$p=0.0105$）．一方，すべての肺炎による死亡には，両群間での有意差を認めなかった．

一方，著者らはこれまでに厚生労働省班会議（班長：岡部信彦）事業として，インフルエンザワクチン定期接種下の65歳以上の786名の高齢者に対する，PPV23接種の臨床効果および肺炎医療費効果に関するオープンラベル無作為比較試験を実施した[13]．この臨床研究においても，75歳以上の高齢者，自立歩行困難な高齢者においてすべての肺炎の発症頻度，入院頻度の有意な減少を認めた．また，全研究参加者において，接種後1年間のワクチン費用を含むすべての肺炎の有意な医療費削減効果が明らかになった．

おわりに

わが国における PPV23 の接種率は 7.8％と低迷しているものの 2010 年 4 月までに，公費負担を行う地方自治体は 224 カ所の市区町村(全国の 12％を占める)となり，着実に増加していることも事実である．今後，わが国で明らかになった高齢者における PPV23 接種による肺炎予防効果，肺炎医療費の削減効果のエビデンスから，高齢者における PPV23 の定期接種化(公費補助)の実現が急務である．また，今後の複数回接種の承認のために，安全性・免疫原性のエビデンスを蓄積する必要がある．

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講　座　呼吸器疾患の新治療

23価肺炎球菌莢膜多糖体ワクチン（ニューモバックス®）の新たなエビデンス

田村　和世　　大石　和徳

要　旨　これまで，わが国において23価肺炎球菌莢膜多糖体ワクチン（ニューモバックス®）は任意接種のままであり，また再接種承認の遅れなどにより接種率が低迷していた。しかしながら，最近になってわが国の臨床研究で本ワクチンの高齢者における肺炎発症予防効果，死亡率の低下，医療費削減効果が明らかになった。今後，高齢者の健康増進，高齢化社会に伴う医療費抑制対策として，本ワクチンの定期接種化（公費助成）の実現と飛躍的な接種率向上が望まれる。

田村 和世　大石 和徳：23価肺炎球菌莢膜多糖体ワクチン（ニューモバックス®）の新たなエビデンス，呼吸 29（10）：996—1001，2010
キーワード：肺炎球菌ワクチン　莢膜多糖体　高齢者　予防

Ⅰ．はじめに

23価肺炎球菌莢膜多糖体ワクチン（ニューモバックス®，以下PPV23と略す）は成人を対象とした肺炎球菌ワクチンである。米国疾病予防管理センター（CDC/ACIP）は，65歳以上の高齢者，65歳未満の易感染者（脾機能不全，心・呼吸器の慢性疾患，糖尿病，腎不全，アルコール依存症，慢性肝障害，脳脊髄液漏，その他HIV感染や白血病などの免疫不全者）に対してPPV23接種を推奨している[1]。日本では1988年に認可されたが，高齢者に対する接種が普及している欧米と比較してわが国の接種率はいまだ約7.8％と明らかに低い。本稿では，PPV23接種の対象である成人（特に高齢者）にとっての肺炎球菌感染症の重要性，PPV23の免疫誘導機構や臨床効果について解説し，わが国での接種率低迷の原因について考え，今後の普及につなげたいと思う。

New evidences for 23-valent pneumococcal capsular polysaccharide vaccine
大阪大学微生物病研究所感染症国際研究センター，高病原性感染症研究部門
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Ⅱ．成人における肺炎球菌感染症の疫学

肺炎球菌は肺炎，髄膜炎，敗血症といった侵襲性感染症の原因となり，特に小児と高齢者にとって高リスクである。2005年のわが国における死亡率の病因別割合では，悪性新生物，心疾患，脳血管障害についで肺炎が第4位を占める。さらにその90％以上が65歳以上の高齢者である（厚生労働省統計；2006年人口動態統計）。

成人の市中肺炎の原因菌としては肺炎球菌が最も多く，わが国での報告では20～30％，諸外国の報告では文献により差があるが5～58％[2]となっている。院内肺炎においては，市中肺炎よりも肺炎球菌肺炎のリスクは減るものの5～20％を占めるとされる。また，施設入所高齢者の肺炎

の原因としては肺炎球菌が18％を占めるとの報告がある[3]。さらに，慢性閉塞性肺疾患(COPD)急性増悪の原因微生物も10～15％が肺炎球菌によるものとされる。抗菌薬が普及した現代においても，耐性肺炎球菌の増加や種々の疾患に対する免疫抑制療法の普及，高齢化などを考慮すると肺炎球菌は依然として重要な病原体であり，侵襲性感染症や肺炎の予防対策の強化が求められる。

Ⅲ．肺炎球菌の病原性とPPV23の液性免疫誘導機構

肺炎球菌は連鎖球菌属に属するグラム陽性双球菌で，表面を多糖体からなる莢膜に覆われている。肺炎球菌を有する多くの病原因子のなかでも，最も重要とされるのがこの莢膜多糖体である。その機能として，気道の分泌粘液による物理的クリアランスに抵抗し気道上皮表面への移行を助けること，貪食細胞に莢膜多糖体を認識する受容体がないこと，貪食細胞に対する電気化学的反発力，抗細胞壁抗体や補体の細胞壁へのアクセス阻害，補体の不活化，自己融解や抗菌薬への曝露からの逃避[4)~6)]などが判明している。

莢膜多糖体の抗原性により，肺炎球菌は現在少なくとも93種類の血清型に分けられており，PPV23はそのうち23血清型の多糖体に対するワクチンである。日本の成人における報告では，侵襲性肺炎球菌感染症患者303人から分離された肺炎球菌のうちPPV23に含まれる血清型が85.4％を占める[7)]。また，別の報告によると，成人肺炎球菌肺炎患者114人からの分離株のうちPPV23に含まれる血清型は82.5％となっている[8)]。

蛋白質抗原に対する抗体産生応答がMHC class Ⅱを介したT細胞補助に依存するのに対し，莢膜多糖体はT細胞の補助なしにB細胞に抗体産生を起こさせるT細胞非依存性抗原(TI抗原)である。TI抗原はリポポリサッカライド(LPS)に代表されるTI-1抗原と多糖体のようなTI-2抗原に大別される。TI抗原が産生するのは主にIgMであり，免疫グロブリンのクラススイッチや親和性の成熟，免疫記憶は殆ど誘導されない。しかしTI-2抗原は次のような補助シグナルの存在によりB細胞にクラススイッチを誘導し，有効な特異抗体産生を誘導することができる(**図1**)。それはToll-likeレセプター(TLR)を介したシグナルや，NK細胞やマクロファージ等が産生するGM-CSF，IFN-γなどのサイトカインであることが分ってきた[9)~11)]。肺炎球菌のように抗貪食作用を有する細菌は，貪食細胞による直接的破壊のみでなく特異的T細胞を誘導するための抗原提示も免れるため，T細胞の補助なしに迅速に抗体を大量産生する機構が重要な役割をもっていると考えられる。PPV23はこのようにして莢膜多糖体に対する血清型特異的液性免疫を誘導し，菌体に結合した血清型特異IgG抗体は補体依存性の貪食殺菌(オプソニン)活性を示す。

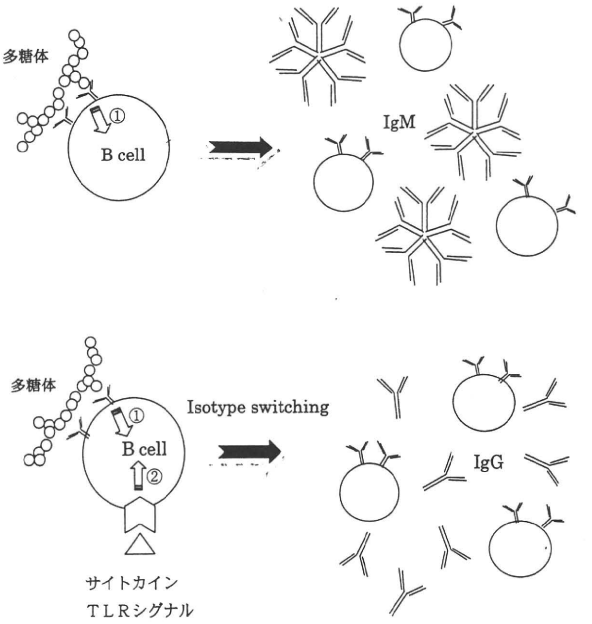

図1　TI-2抗原による免疫応答
TI-2抗原である多糖体は，それだけでは有効な抗体産生をしないが(上図)，マクロファージやNK細胞から産生されるサイトカインやTLRシグナルの補助(②)のもとで有効な抗体産生をするようになる(下図)。

Ⅳ．PPV23接種の現状

わが国では，まだ65歳以上の推定人口(2009年10月時点，2,821万人)の7.75％がPPV接種を受けているにすぎない(**図2**)。普及が進んでいない原因として，これまで肺炎予防効果についてのエビデンスが乏しかったこと，再接種が昨年秋まで認められていなかったため，より高齢になるまで接種を控える傾向にあったことなどが考えられる。これらについては，後述のようにわが国での臨床試験にて高齢者に対する肺炎予防効果，死亡率減少効果が証明されたこと，再接種が可能となったことの認識が広まれば改善されると思われる。しかし問題はそれだけではなく，わが国では脾摘患者の肺炎予防を除いてPPV23接種は全額自己負担となり，1回当たり6,000～9,000円の費用がかかることが高齢者にとって大きな負担となっている(米国での50％を超える高い接種率の背景には，PPV23接種がメディケアなどの民間保険で負担されている事実がある)。2010年8月11日現在では公費助成を行う自治体数は293市区町村に増加しているが，一方で地方財政の悪化などにより助成を打ち切る自治体も出てきている(**図3**)。

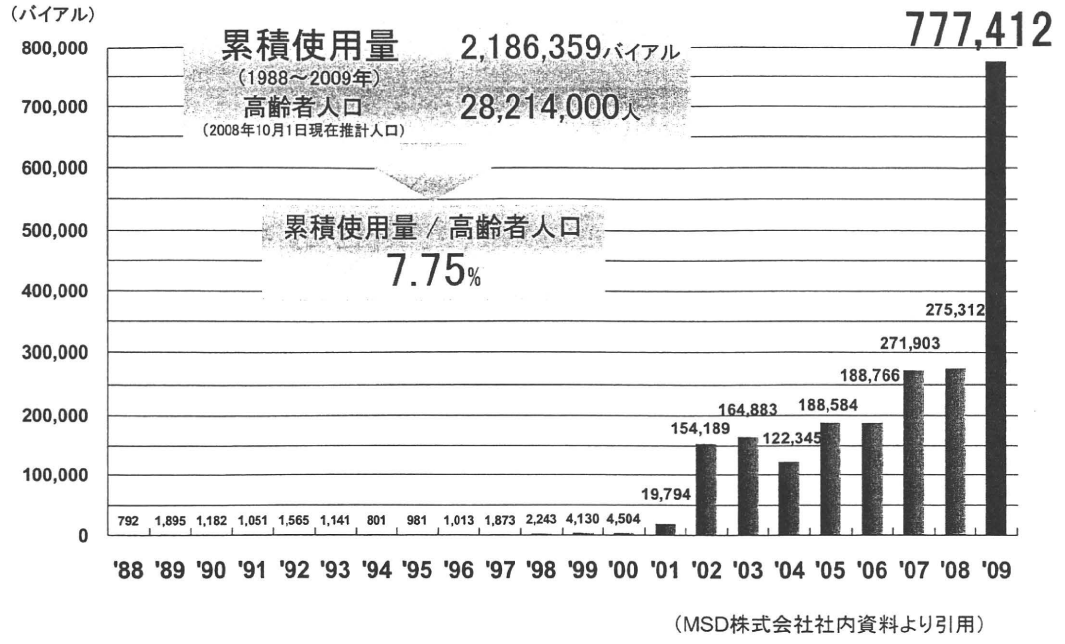

図2　23価肺炎球菌ワクチン年次別使用量の推移(1988～2009年)

図3　23価肺炎球菌ワクチン公費助成の状況(MSD株式会社社内資料より引用)

表1　日本のナーシングホーム居住者の23価肺炎球菌莢膜多糖体ワクチン接種群とプラセボ群における肺炎罹患率，死亡率の比較

	罹患頻度(1,000人/年)		罹患減少率(%)(95%CI)	p値
	ワクチン接種群(n=502)	プラセボ群(n=504)		
肺炎球菌肺炎	12	32	63.8 (32.1～80.7)	0.0015
非肺炎球菌肺炎	43	59	29.4 (−4.3～52.3)	0.0805
すべての肺炎	55	91	44.8 (22.4～60.8)	0.0006

	死亡率(%)		p値
	ワクチン接種群(n=502)	プラセボ群(n=504)	
肺炎球菌肺炎	0/14(0)	13/37(35.1)	0.0105
非肺炎球菌肺炎	13/49(26.5)	13/67(19.4)	0.3632
すべての肺炎	13/63(20.6)	26/104(25.0)	0.5181

23価肺炎球菌莢膜多糖体ワクチン接種群では肺炎球菌肺炎，すべての原因の肺炎においてプラセボと比較して優位に罹患頻度が減少し，予防効果が示された。また，肺炎球菌肺炎における死亡率を有意に減少させた。
(Maruyama K, *et al*[16]. *BMJ* 340：2010より引用)

Ⅴ．PPV23の臨床効果

1993年から14年間にわたり，米国CDCの協力のもと行われた追跡調査の結果，PPV23の含有株に対する肺炎球菌感染症が基礎疾患を有する易感染性患者において証明された[13]。その後成人肺炎については，PPV23接種による生存率の改善効果や重症化予防効果が報告[14]されたが，肺炎発症予防効果としては65歳以下のCOPD患者あるいは予測1秒量40％以下の高度な気流閉塞を伴うCOPD患者[15]という限られた集団でのものであり，肺炎発症予防効果のエビデンスは乏しかった。最近になって，日本の1,006人の高齢者介護施設入所者(平均年齢85歳)を無作為にPPV23接種群(502人)と非接種群(504人)に割りつけ，肺炎，肺炎球菌肺炎の発症および死亡について二重盲検試験で3年間比較検討した結果が報告された(**表1**)[16]。これによると，PPV23接種群では肺炎球菌肺炎のみならず，すべての肺炎に対する予防効果が認められ，PPV23は肺炎球菌肺炎の死亡率を有意に減少させた。

一方，国内のインフルエンザワクチン定期接種を受けた65歳以上の高齢者786人を対象として，PPV23接種群(391人)と非接種群(387人)の2群に割りつけたオープンラベル無作為比較試験の結果も報告されている[17]。本研究において，65歳以上の高齢者全体では両群に肺炎の発症，肺炎による入院頻度に有意な差は認められなかったものの，75歳以上の高齢者では1年間の肺炎発症リスクがPPV23接種群で有意に減少し，歩行困難者においては2年間の肺炎発症リスクがPPV23接種群で有意に減少した。また75歳以上の高齢者，歩行困難者とも2年間の肺炎による入院頻度がPPV23接種により有意に減少した。さらに，65歳以上の高齢者全体においてPPV23接種群ですべての肺炎による医療費も有意に削減された(1年間，1人当たり76,000円)(**表2**)。

このように，わが国における大規模な無作為比較試験により国内外で高齢者における肺炎予防効果，死亡率の低下効果，医療費削減効果が示されたことから，少なくとも75歳以上の高齢者に対する本ワクチン接種が推奨される。

Ⅵ．PPV23の副作用

PPV23の副反応として，一般に発熱，注射部位の疼痛，発赤，腫脹がみられるが，注射部位の発赤，腫脹は数日以内に軽快し，生命予後に影響する重篤な副作用は報告されていない。一方，PPV23の再接種は2009年10月になってようやく承認された。初回接種から5～6年が経過した慢性肺疾患患者に対しPPV23を再接種した場合に，12％に接種後1週間以内の発熱，8～65％に局所の腫脹・発赤が認められたが，これらの副反応は無治療で再接種6日以

表2 日本の高齢者に対するPPV23接種群と非接種群におけるすべての肺炎による入院頻度，医療費削減効果の比較

すべての肺炎による入院頻度の減少効果(2年間)

	入院エピソード数		減少率(%) (95 % CI)	p値
	ワクチン接種群	ワクチン非接種群		
65歳以上	60	76	41.2(2.7～65.5)	0.183
75歳以上	46	67	41.5(2.7～65.5)	0.039
歩行困難例	16	42	62.7(25.7～82.1)	0.005

すべての肺炎による医療費削減効果(1年間)

	医療費(円)		削減額(円) (95 % CI)	p値
	ワクチン接種群	ワクチン非接種群		
65歳以上	57,385	140,875	76,015(1,955～149,960)	0.027
75歳以上	68,655	200,215	124,085(15,640～232,530)	0.018
歩行困難例	148,350	619,505	463,680(97,635～829,725)	0.013

〔Kawakami K, *et al*[17]. *Vaccine*：2010(in press)より引用〕

内に改善している[18]。

Ⅶ. 予防接種法改正の動向とPPV23

現在，厚生労働省は厚生科学審議会予防接種部会において，その委員の任期満了(平成24年3月)までに，予防接種法の定期接種の対象疾患の追加について検討を進めている。具体的には9つのワクチン(Hibワクチン，PPV23，7価肺炎球菌コンジュゲートワクチン，ヒトパピローマワクチン，水痘ワクチン，ムンプスワクチン，B型肝炎ワクチン，ポリオワクチン，百日咳ワクチン)が検討対象になっているが，成人のみを対象とするワクチンはPPV23のみである。

一方，予防接種法改正の動向を受けて，日本医師会と予防接種推進専門協議会は，PPV23を除く8ワクチンが小児において定期接種化されることを目指して「小児ワクチンキャンペーン」を展開中である。このような国内のワクチン行政の動向から，筆者ら内科医(呼吸器内科医，感染症内科，一般内科を含む)にとって明確なアピールをすべき時期に差しかかっていると思われる。わが国で示された高齢者に対するPPV23の効果のエビデンスを軸に成人用肺炎球菌ワクチンキャンペーンを加速させる必要があろう。

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肺炎球菌ワクチン

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〔論文要旨〕

肺炎球菌感染症は侵襲性感染症と菌血症を伴わない肺炎とに大別され，その多くは菌血症を伴わない肺炎である．わが国における小児の肺炎球菌による侵襲性感染症の原因菌の主要な血清型は6B，19F，24，23Fなどである．一方，成人における侵襲性感染症の原因菌の主要血清型は12F，3，6B，14，4，23Fであるのに対し，市中肺炎の原因菌では19F，23F，6B，3，14であり，血清型分布が病型により異なる．

わが国では，成人用23価肺炎球菌ポリサッカライドワクチン（PPV23）と小児用7価肺炎球菌コンジュゲートワクチン（PCV7）が臨床承認されている．また，現在PCV13の小児，成人に対する臨床応用が検討されている．これらのポリサッカライドベースのワクチンの免疫原性について，ELISAによる血清型特異IgG測定とOpsonophagocytic assay（OPA）による血清型特異的なオプソニン活性の評価が可能である．今後，小児，成人における特異IgG定量のみならずオプソニン機能の評価が必要と考える．

PCV7の導入以来，欧米諸国における乳幼児の侵襲性感染症に対する劇的な予防効果が示され，また肺炎や中耳炎に対する予防効果も明らかになった．さらには，小児におけるPCV7のカバー率が90％に達する条件下では，65歳以上の高齢者における侵襲性感染症が減少するという，集団免疫効果も明らかになった．しかしながら，PCV7に含有されない血清型による侵襲性感染症の増加とこれらの血清型にペニシリン非感受性菌が増加していることも報告されている．また，この効果は先進国以上にアフリカをはじめとする発展途上国における乳幼児に対する効果が期待されている．このような背景から，わが国においても厚生労働省は小児に対するPCV7の公費助成の方針を2010年10月に決定した．

一方，PPV23はこれまで成人における侵襲性感染症に対する臨床効果が明らかにされていたが，高齢者における肺炎に対する効果が明らかでなかった．しかしながら，最近になってわが国における高齢者に対する肺炎球菌性肺炎，すべての肺炎に対する予防効果，肺炎球菌性肺炎による死亡率の低下，また肺炎による医療費削減効果が明らかになった．今後，高齢者に対するPPV23の定期接種化の実現が望まれる．

1. はじめに

肺炎球菌は1881年に初めて分離培養され，1980年代には大葉性肺炎の主要な原因菌であることが判明した．その後，1904～1910年には免疫血清によるオプソニン活性，血清型特異的免疫応答が明らかになり，1911年には南アフリカにおいて，全菌体ワクチンの臨床試験が開始されている．現在，成人に臨床応用されている23価肺炎球菌ポリサッカライドワクチン（PPV23）

Pneumococcal Vaccine

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