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A Japanese nationwide survey of 23-valent pneumococcal capsular polysaccharide vaccine (PPSV23) coverage among patients with chronic medical condition aged 50 and older

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ABSTRACT

The 23-valent capsular polysaccharide pneumococcal vaccine (PPSV23) was introduced in Japan's routine immunization schedule October 2014. It was recommended for adults aged 65 years (including those ≥65 during the transition period), and for adults 60–64 with cardiac, renal, or respiratory dysfunction equivalent to Level 1 physical disability. Several studies have shown that patients aged 50+ with chronic medical conditions (CMC) are at elevated risk of pneumococcal infection. Nonetheless, PPSV23 vaccination rates among this population remains low. In our study, we report the results of a survey investigation into PPSV23 vaccination rates among Japanese patients aged 50+ with CMC. Patients aged 50+ comprised the patient population (n = 5,078) and internal medicine physicians comprised the doctor population (n = 400) located all over Japan were asked an array of questions relevant to PPSV23 immunization in June 2018 via Web-based surveys. PPSV23 coverages among chronic patients aged 50–59, 60–64, and 65+ years were respectively 1.3%, 2.9%, and 37.8%. The high disease-specific PPSV23 rates seen in the 65+ group was 50.0% and 49.4%, for chronic liver disease and chronic lung disease, respectively. Doctors most frequently cited a lack of municipal subsidies as justification for recommending the vaccine to patients with CMC aged 50–64 years, and deference to patients' wishes as justification for patients with CMC aged 65+. In conclusion, PPSV23 has poor coverage among Japanese adults aged 50–64 with CMC. Doctors and local authorities need to raise public awareness to improve the vaccination rate, given the high risk of pneumococcal infectious disease among patients with CMC.

Introduction

Pneumococcal disease, caused by infection with the bacteria *Streptococcus pneumonia*, is a leading cause of community-acquired pneumonia, meningitis, sepsis and bacteremia worldwide.[1] Young children and the elderly are especially prone to two forms of pneumococcal disease – pneumococcal pneumonia (PP) and invasive pneumococcal disease (IPD) – as are immunocompromised persons with limited ability to produce antibodies against capsular polysaccharides, such as those with HIV or cancer.[2,3] IPD rates among individuals with chronic medical conditions (CMC) or immunosuppression are between three to six times higher than in healthy adults[4] the risk is even higher in individuals with multiple comorbid CMC. Studies have found associations between chronic disease and pneumonia severity in Japanese populations as well.[5]

Two types of adult pneumococcal vaccines containing capsular polysaccharides are available in Japan today. The first is the 23-valent capsular polysaccharide pneumococcal vaccine, PPSV23 (Pneumovax®NP Merck & Co., Inc., Kenilworth, NJ, USA), which consists of capsular polysaccharides from 23 serotypes of *S. pneumoniae* and was approved in 1988 for individuals aged 2 or older, including the elderly aged 65 years and older, at high risk of

serious illness due to pneumococcal infection. The second is the 13-valent pneumococcal conjugate vaccine, PCV13 (Prevenar13® Pfizer Inc., New York, USA), a pneumococcal conjugate vaccine consisting of 13 capsular polysaccharides covalently bound to detoxified diphtheria toxins (toxoids). In 2013, PCV13 was approved for children between 2 months and 6 years old and introduced into Japan's routine immunization schedule; the following year (2014), it was approved for adults 65 years and older. In October 2014, PPSV23 was introduced into Japan's routine immunization schedule and was recommended for adults aged 65 years and older, and for adults aged 60–64 years with cardiac, renal, or respiratory dysfunction or immunodeficiencies which result in significant functional impairment, defined as a level 1 physical disability in Japan. Public subsidies were introduced at the same time to partially cover vaccination costs.[6]

Many countries recommend pneumococcal vaccination for at-risk groups to reduce the public health burden of pneumococcal disease.[7,8] In the United States, for example, PPSV23 is recommended for patients aged 19 to 64 with certain CMC. One U.S. longitudinal study conducted from 2009–2013 reported PPSV23 vaccination rates of 8% at 1-year follow-up, and 20.1% at 5-year follow-up, among adults aged 19–64 with diabetes mellitus, chronic heart, lung, or liver disease.[9]

Cross-sectional studies have variously estimated PPSV23 coverage at 9.1% among patients with CMC aged 50–64 in Spain's Catalonia region in 2015,[10] and of 12.2% and 21.8% among patients with CMC aged 19–64 and 65+, respectively, in South Korea in 2013.[11]

In Japan, Imai et al. used two health insurance claims databases to compare PP and IPD prevalence between individuals with and without CMC in an observational study. They found that patients with CMC were at greater risk for pneumococcal disease than adults without CMC, and that patients with CMC aged 50 to 64 years and older were at higher risk for pneumococcal infection than those aged ≥65 without an underlying condition.[12]

In two recent IPD surveillance studies in Japan, more than half of confirmed cases were immunosuppressed, or had some forms of CMC, with a wide range of diseases represented.[13,14] Chronic diseases can cause serious harm after their initial development, with many patients experiencing serious sequelae and even death. Despite recent reports of elevated pneumococcal infection risk among patients with CMC in Japan,[12] we still don't have a complete picture of pneumococcal vaccination rates among this demographic after age 50, when they become increasingly susceptible to pneumococcal infection.

Data on PPSV23 coverage among patients with CMC would serve as an important resource in discussions about how to prevent pneumococcal disease in this population. In addition, identifying specific factors that encourage or predict PPSV23 vaccination could provide useful knowledge and suggestions for further improving coverage.

In this paper, we report the findings of a survey designed to determine PPSV23 vaccination rates among Japanese adults aged 50 and older with CMC, as well as the reasons their doctors give for not recommending immunization.

Material & methods

Survey overview

This investigation was conducted in June 2018 via Macromill Carenet, a web-based survey company, using a cross-sectional design. Separate questionnaires were administered to patients 50 years and older ("patients") and internal medicine physicians ("doctors") registered in online survey panels managed by Macromill Carenet. Both patients and doctors completed the surveys online.

Patient survey

The patient survey was sent to approximately 140,000 Japanese men and women 50 years and older located all over the country and administered 5,000, who were able to complete the internet survey, in three age groups: 50–59, 60–64, and 65+. Regular hospital/clinic visits at least once in 6 months was the only other condition for adults in the first two groups. In the third, elderly adults were selected using stratified sampling by age and sex, regardless of current medical care, to ensure the corresponding ratios in the dataset matched 2018 estimates for all Japanese adults aged 65 and older. Eligible patients provided consent electronically. Questionnaire included questions about CMC; pneumonia history (yes/no); pneumococcal vaccination history (yes/no), pneumococcal vaccine type (PPSV23/PCV13/Unknown), and count(s); whether they had been recommended the vaccine by their doctor; whether they had received a vaccine subsidy or notification from their local government; influenza vaccination history (2017/2018 season); and background characteristics (height, weight, and smoking, drinking, and exercise habits).

CMC was defined as any of the following in reference to the 2017 recommended immunization schedule issued by the U.S. Advisory Committee on Immunization Practices (ACIP),[15] including hypertension as a Japanese typical chronic medical condition: chronic heart disease (e.g. congestive heart failure, cardiomyopathy, and hypertension), chronic lung disease (e.g. chronic obstructive lung disease, emphysema, asthma), diabetes mellitus, alcoholism, chronic liver disease (e.g. cirrhosis), cigarette smoking, chronic kidney disease, cerebrospinal fluid leak, cochlear implant, HIV (AIDS), cancer, organ transplantation, and anatomical or functional asplenia.

Outcomes assessed were PPSV23 coverage rate among all patients with at least one chronic medical condition (primary) and disease-specific vaccine coverage rates. ORs for CMC, age groups and other background variables were calculated.

Doctor survey

The doctor survey was sent to approximately 100,000 Japanese internal medical doctors located all over the country. Four hundred doctors that provide care for at least 100 patients aged 50+ years per month were enrolled from a nationwide database to complete the internet survey. Eligible doctors provided consent electronically. Questionnaire assessed reasons for not recommending pneumococcal vaccination to patients of two age groups with CMC (50–64 and 65+ years).

Statistical analysis

PPSV23 coverage among patients with CMC was calculated as the ratio of PPSV23-vaccinated patients with CMC to all patients with CMC by age group (50–59, 60–64, and 65+ years).

Disease-specific PPSV23 rates were calculated as the ratio of PPSV23-vaccinated patients with a given condition to all patients with the same condition, for the entire sample and by age group. PPSV23 coverage was also calculated for adults aged 65+ with and without CMC.

Crude ORs and corresponding 95% Confidence Intervals (CIs) were calculated for several variables to determine their predictive value for PPSV23-vaccinated status: disease type, subsidy availability, doctor's recommendation, and background characteristics (gender, BMI, pneumonia history, influenza vaccination, and alcohol, tobacco, and exercise habits). Factors identified as significantly associated with PPSV23 vaccination were further explored using multivariate logistic regression, with model selection using the stepwise method, and adjusted ORs (AORs) calculated accordingly. Doctors' reasons for not recommending the pneumococcal vaccination for patients with CMC were analyzed using descriptive statistics, separately for those they see aged 50–64 and 65+. IBM SPSS Statistics 24.0 was used for all analyzes.

Ethics approval

This study was approved by the ethics review board of the Medical Corporation Toukeikai Kitamachi Clinic (June 19, 2018), and registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000033094).

Results

Patients' demographics and health characteristics

The patient survey was administered to 5,078 Japanese men and women 50 years and older located all over the country, who were able to complete the internet survey, in three age groups: 50–59 (n = 1,700), 60–64 (n = 1,700), and 65+ (n = 1,678). Regular hospital/clinic visits at least once in 6 months was the only other condition for adults in the 50–59 and 60–64 groups. In the 65+ group, elderly adults were enrolled using stratified sampling by age and sex, regardless of current medical care, to ensure the corresponding ratios in the dataset matched 2018 estimates for all Japanese adults aged 65 and older. Table 1 shows the demographic and health characteristics of respondents by vaccination status and age group. Among respondents with regular hospital/clinic visits, CMC were present in 57.8% of patients aged 50–59 years old, 72.7% of patients aged 60–64 years old, and in 83.2% of patients aged 65 years and older. In the 65+ group, 664/1,678 patients did not have a CMC. Among CMC patients, patients with 2 or more CMC were 51.4% in aged 50–59 years old, 49.7% in aged 60–64 years old, and 60.6% in aged 65 years and older. Additionally, immunocompromised patients having chronic renal disease, cancer, organ transplantation, hematopoietic stem cell transplantation, AIDS/HIV infection, cochlear implant, cerebrospinal fluid leakage or splenectomy defined in ACIP recommendation[15] were 12.3%, 11.8% and 12.9% in each aged group, respectively.

There is a significant association between PPSV23 vaccination status and history of pneumonia and influenza vaccination across all age groups; while PPSV23 vaccination status is significantly associated with regular exercise in the 50–59 and 60–64 years old cohorts, and with regular alcohol and regular smoking in 50–59 and 65+ years old cohorts.

Coverage rates among patients with CMC

PPSV23-specific coverage rates in the 50–59, 60–64, and 65+ groups were respectively 1.3%, 2.9%, and 37.8% (Figure 1).

Noting that many respondents were unable to identify the specific type of pneumococcal vaccine they received, nonspecific pneumococcal vaccine coverage rate among patients with CMC was 1.8%, 4.4% and 54.9% for age groups 50–59, 60–64 and 65+ respectively.

Figures 2 and S1 show disease-specific PPSV23 rates among elderly (age 65+) patients with CMC, and for all age groups, respectively. PPSV23 coverage rate was the highest among elderly patients with chronic liver disease (50.0%), followed by chronic lung disease (49.4%). On the other hand, PPSV23 rates among elderly with cancer or chronic kidney disease was lower than the cohort average (respectively, 33.0% and 31.3% vs. 37.8%). All disease-specific rates were higher than for patients without a chronic medical condition (23.0%).

Factors associated with PPSV23 vaccination among patients with CMC

Tables 2 and 3 show the results of multivariate logistic regression analysis for PPSV23 vaccination rates among patients with CMC in the 65+ (Table 2) and 50–59 and 60–64 age groups (Table 3). First, crude odds ratios (ORs) for PPSV23-vaccinated status were calculated separately for each independent variable (disease, background characteristics). Next, multivariate analysis was used to identify significant predictors in a logistic regression model, with associated adjusted odds ratios (AORs). The most influential factors among patients with CMC aged 65+ were, in descending order, municipal subsidies/notifications (AOR: 5.47), doctors' recommendation (4.09), and past influenza vaccination (1.98). Chronic lung disease seemed to positively predict PPSV23 vaccination (1.56), although this trend was not statistically significant.

Table 1. Demographics and Health Characteristics of Japanese aged 50+ respondents with CMCs who vaccinated and unvaccinated the PPSV23 (n = 3,232).

	50–59 (CMC+)					60–64 (CMC+)					65+ (CMC+)				
	PPSV23 Vaccinated		PPSV23 Unvaccinated			PPSV23 Vaccinated		PPSV23 Unvaccinated			PPSV23 Vaccinated		PPSV23 Unvaccinated		
	13	(%)	969	(%)	p value	36	(%)	1200	(%)	p value	383	(%)	631	(%)	p value
Female	3	(23.1)	429	(44.3)	0.1262	21	(58.3)	549	(45.8)	0.1356	186	(48.6)	284	(45.0)	0.2709
Regularly Consume Alcohol	11	(84.6)	340	(35.1)	0.0002	9	(25.0)	467	(38.9)	0.0909	99	(25.8)	218	(34.5)	0.0038
Regularly Smoking	8	(61.5)	231	(23.8)	0.0017	7	(19.4)	245	(20.4)	0.8866	20	(5.2)	71	(11.3)	0.0011
Exercise	9	(69.2)	228	(23.5)	0.0001	19	(52.8)	406	(33.8)	0.0184	186	(48.6)	294	(46.6)	0.5422
BMI <20	3	(23.1)	143	(14.8)	0.4023	10	(27.8)	197	(16.4)	0.0721	68	(17.8)	91	(14.4)	0.157
History of pneumonia over aged 50	3	(23.1)	46	(4.7)	0.0026	12	(33.3)	70	(5.8)	<0.0001	42	(11.0)	37	(5.9)	0.0033
Flu vaccinated	12	(92.3)	292	(30.1)	<0.0001	20	(55.6)	397	(33.1)	<0.0001	241	(62.9)	248	(39.3)	<0.0001

※CMC+:Chronic medical conditions, visiting hospital or clinic for treatment of following diseases: Chronic heart disease, Chronic lung disease, Diabetes mellitus, Chronic liver disease, Chronic renal disease, Cancer, etc.
※Regularly Consume Alcohol: Drinking two and more cup of sake every day, The one cup of sake (180 ml) is almost equivalent to the following amount. One bottle of beer (5% of alcohol, 500 ml), 0.6 cup of shochu (25% of alcohol, 110 ml), 1/4 bottle of wine (14% of alcohol, 180 ml), One cup of whiskey (43% of alcohol, 60 ml), 1.5 canned beer (5% of alcohol, 520 ml)
※Regularly Smoking: Smoking every day or occasionally
※Exercise: To exercise more than 30 minutes per time twice a week and it has been continuing for more than 1 year
※Flu vaccinated: 2017, 2018 vaccinated
※p value: Calculated by Chi-squared test, Statistical significance was set at p < 0.05 (2-tailed)

Figure 1. Coverage rate of PPSV23 among those having CMCs in each age group (n = 3,232). CMC+: Chronic medical conditions, visiting hospital or clinic for treatment of following diseases: Chronic heart disease, Chronic lung disease, Diabetes mellitus, Chronic liver disease, Chronic renal disease, Cancer, etc.
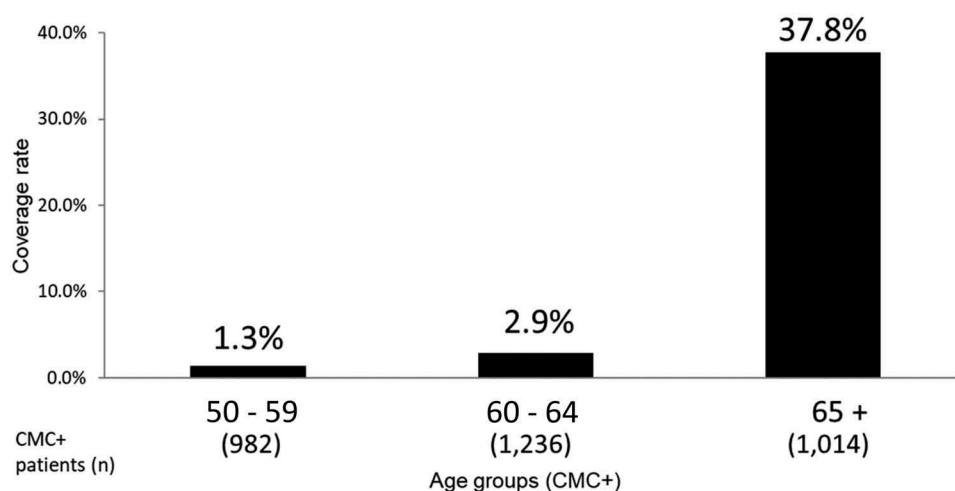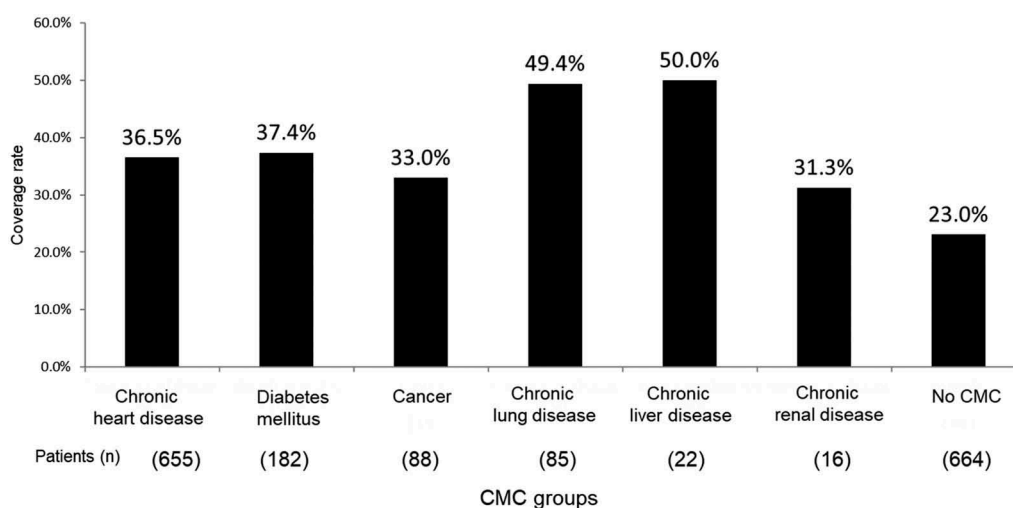

Figure 2. Coverage rate of PPSV23 among each CMC groups and no-CMC group in aged 65+ (n = 1,712). CMC: Chronic medical conditions, visiting hospital or clinic for treatment of following diseases: Chronic heart disease, Diabetes mellitus, Cancer, Chronic lung disease, Chronic liver disease, Chronic renal disease.

Table 2. Factors associated with PPSV23 vaccination who those having CMCs in aged 65+.

	65+					
	Unadjusted OR	95% CI	p value	Adjusted OR	95% CI	p value
Sex (Ref male)	0.87	0.67–1.12	0.299			
Regularly Consume Alcohol	0.66	0.50–0.88	0.004	0.63	0.45–0.88	0.006
Regularly Smoking	0.44	0.26–0.73	0.001	0.56	0.32–1.00	0.048
Exercise	1.08	0.84–1.4	0.560			
BMI<20 (Ref BMI ≥20)	1.28	0.91–1.81	0.181			
History of pneumonia over aged 50	1.98	1.25–3.14	0.005			
Flu vaccinated	2.62	2.02–3.41	<0.001	1.98	1.47–2.67	<0.001
Recommendation by doctor	6.16	4.51–8.4	<0.001	4.09	2.93–5.72	<0.001
Municipal government subsidies and notification	6.52	4.80–8.86	<0.001	5.47	3.95–7.58	<0.001
Chronic heart disease	0.86	0.66–1.12	0.279			
Chronic lung disease	1.68	1.08–2.63	0.026	1.56	0.94–2.61	0.086
Chronic renal disease	0.75	0.26–2.16	0.796			
Diabetes Mellitus	0.98	0.70–1.36	0.933			
Chronic liver disease	1.67	0.72–3.88	0.268			
Cancer	0.79	0.50–1.26	0.359			

※Adjusted OR: Factors identified as significantly associated with PPSV23 vaccination were further explored using multivariate logistic regression, with model selection using the stepwise method (α = 0.2), and adjusted OR calculated accordingly
※OR: Odds ratio.

Table 3. Factors associated with PPSV23 vaccination who those having CMCs in aged 50–59 and 60–64.

	50–59						60–64					
	Unadjusted OR	95% CI	p value	Adjusted OR	95% CI	p value	Unadjusted OR	95% CI	p value	Adjusted OR	95% CI	p value
Sex (Ref male)	2.65	0.72–9.68	0.163				0.60	0.31–1.18	0.174			
Regularly Consume Alcohol	10.18	2.24–46.17	<0.001	3.67	0.98–13.82	0.054	0.52	0.24–1.12	0.117			
Regularly Smoking	5.11	1.66–15.78	0.004				0.94	0.41–2.17	1.000			
Exercise	7.31	2.23–23.97	0.001				2.19	1.12–4.25	0.021	1.97	0.89–4.38	0.095
BMI <20 (Ref BMI ≥20)	1.73	0.47–6.37	0.424				1.96	0.93–4.13	0.108			
History of pneumonia over aged 50	6.02	1.60–22.62	0.023	5.65	1.08–29.62	0.041	8.07	3.88–16.81	<0.001	2.61	0.89–7.67	0.081
Flu vaccinated	27.82	3.60–214.96	<0.001	4.85	1.22–19.33	0.025	2.53	1.30–4.93	0.007			
Recommendation by doctor	642.67	134.90–3061.67	<0.001	126.68	29.99–535.08	<0.001	68.79	28.10–168.38	<0.001	23.48	7.18–76.78	<0.001
Municipal government subsidies and notification	85.69	19.71–372.51	<0.001				30.93	13.79–69.36	<0.001	20.56	8.88–47.62	<0.001
Chronic heart disease	1.26	0.42–3.77	0.783				0.83	0.43–1.61	0.613			
Chronic lung disease	2.17	0.47–9.96	0.271				1.19	0.36–3.97	0.738			
Chronic renal disease	2.91	0.37–23.17	0.315				4.98	1.09–22.79	0.077	4.45	0.58–33.98	0.150
Diabetes Mellitus	1.92	0.59–6.31	0.284				0.71	0.28–1.86	0.662			
Chronic liver disease	6.11	1.29–28.87	0.057	7.13	0.86–59.13	0.069	1.96	0.45–8.48	0.293			
Cancer	1.44	0.18–11.29	0.523				0.38	0.05–2.81	0.508			

※Adjusted OR: Factors identified as significantly associated with PPSV23 vaccination were further explored using multivariate logistic regression, with model selection using the stepwise method (α = 0.2), and adjusted OR calculated accordingly.
※OR: Odds ratio.

Significant predictive factors of PPSV23 vaccination included doctors' recommendation, past influenza vaccination, and recent pneumonia history (at age ≥50) in the 50–59 group and doctors' recommendation and municipal subsidies/notifications in the 60–64 group.

Doctors recommending or not recommending pneumococcal vaccination to patients with CMC

Figure 3 illustrates doctors' attitudes toward recommending pneumococcal vaccination to patients with CMC in two different age brackets (50–64 and 65+ years). For both age groups, majority of doctors claimed to only recommend the vaccine if their patients specifically requested it. Doctors actively recommended the pneumococcal vaccine more often to patients aged 65+ with CMC compared patients aged 50–64 years with CMC (37.1% vs. 23.8%).

Specific rationales for not recommending pneumococcal vaccines to either age groups are detailed in Figures S2 and S3. 10.8% of doctors did not recommend the vaccine to patients aged 50–64 years with CMC. The most frequently cited reasons for not recommending the pneumococcal vaccines to this patient population are: lack of municipal subsidies (46.5%), deference to patients' wishes (39.5%), and their (mistaken) belief that adult pneumococcal vaccines were only meant for elderly persons aged 65 and older (30.2%). On the other hand, only 3.5% of doctors did not recommend the vaccine to patients aged 65 years and older with CMC. Deference to patients' wishes was the most commonly cited justification (35.7%).

Discussion

In this paper, we describe the findings of an internet survey examining PPSV23 vaccination rates among Japanese adults aged 50 and older with CMC, along with doctors' reasons for not recommending pneumococcal vaccination. To our knowledge, this is the first study to describe pneumococcal vaccination rates among Japanese patients with CMC aged 50 years and older in Japan.

Our estimates above for PPSV23 coverage do not include patients who confirmed they had received a pneumococcal

vaccine but were uncertain whether it was PPSV23 or PCV13. Nonspecific pneumococcal vaccine coverage, including both PCV13 and "unknown" responses, reached 54.9% among elderly patients aged 65+ with CMC. Given how many more respondents claimed to have received PPSV23 than PCV13, the real PPSV23 coverage in this demographic is probably higher than estimated in our study. Similarly, the 1.3% and 2.9% rates seen in the 50–59 and 60–64 age groups were likely underestimated as well, however, there remain low.

Nearly half of elderly adults with chronic liver or lung disease had been vaccinated with PPSV23 in our elderly cohort, compared to around one-third of those with chronic heart disease, diabetes, or cancer. This discrepancy probably doesn't originate from differences in clinical guidance between disease categories: for example, both Japanese Respiratory Society[16] and Japanese Diabetes Society[17] guidelines recommend pneumococcal vaccination for elderly adults. Differences in perceived relevance may be responsible for this. It is reasonable to think that pneumonia and its prevention would be of high concern to a pulmonologist, but potentially not of high priority to an endocrinologist or cardiologist.

Our investigation only included doctors seeing adult patients aged 50 and older on a routine basis. Low coverage among patients with CMC was apparent in all age groups, despite the fact that most doctors claimed to recommend pneumococcal immunization to those with CMC. One major reason was the 'passive' stance toward PPSV23 vaccination reported by most doctors, recommending it only in response to patient inquiries. Justifications doctors cited for not recommending PPSV23 diverged between patients with CMC aged 50–64 and those 65 and older. The availability of financial assistance from local governments, environmental factors, and patients' own beliefs seemed to greatly influence their decisions to not recommend PPSV23 to patients aged 50–64, with many citing lack of municipal subsidies, deference to patients' wishes, and the (mistaken) belief that adult pneumococcal vaccines are only meant for elderly persons aged 65 and older as justification.

Predictors of pneumococcal vaccination among Japanese adults aged 65 and older have previously been studied by two research groups. Sakamoto et al. conducted a survey of elderly club
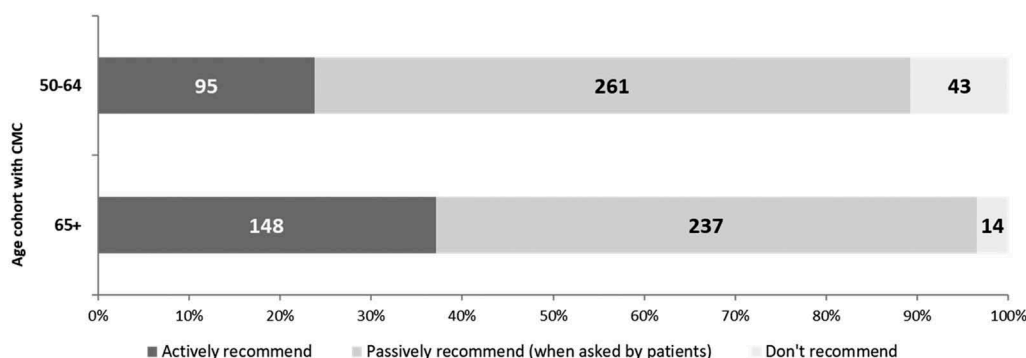
Figure 3. Recommendation of Pneumococcal vaccination to aged 50–64 and 65+ with CMC (Doctor: n = 399). CMC: Chronic medical conditions, visiting hospital or clinic for treatment of following diseases: Chronic heart disease, Chronic lung disease, Diabetes mellitus, Chronic liver disease, Chronic renal disease, Cancer, etc.

members regarding vaccination behaviors and first-time vaccination rates for the pneumococcal vaccine. They found pneumococcal vaccination to be significantly associated with recommendations from medical professionals, past history of influenza immunization, and perceptions of pneumonia severity.[18] In another questionnaire-based study, Higuchi et al. looked at PPSV23 rates and motivations among elderly adults receiving regular outpatient care, and found doctors' advice to positively correlate with vaccinated status.[19] We observed doctors' recommendations to significantly and strongly predict PPSV23-vaccinated status in all three age groups in the present study. In addition, PPSV23's inclusion in Japan's routine immunization schedule for elderly adults appears to have been the major reason for coverage observed in the 65+ age group. Municipal subsidies and notifications were highly associated with vaccinated status among adults aged 60–64 and 65+, but only weakly in our 50–59 subset. We observed greater coverage among patients aged 65 + with chronic lung disease than those with other conditions, echoing associations of PPSV23-vaccinated status with COPD and chronic respiratory failure observed in a cross-sectional study of hospital patients in Spain.[20] Moreover, we observed high associations between regular alcohol consumption and chronic liver disease with PPSV23-vaccinated status in patients aged 50–59. Similarly, Hanada et al. reported a high correlation between chronic liver disease and IPD mortality in an IPD surveillance study.[21]

Our study has several limitations. Our 65-and-older cohort was enrolled using stratified sampling by age and gender, to ensure our sample would be statistically representative of this segment of the Japanese population. We had imagined that 'very-old' (80+) adults might have difficulty participating in an Internet survey; however, we were pleasantly surprised to see that each age stratum in our dataset was close to its ideal size, with plenty of very-old participants (with the caveat that few respondents were 85+). Nonetheless, our methodology still might be a source of bias, since very-old adults capable of using the Internet may be healthier overall. Additionally, still remains a concern that patients who have severe underlying diseases might have no or less internet access regardless of age.

The other limitation is also inherent in our methodology: respondents needed to have the capability to participate in the Web-based survey, although they are still statistically representative of Japan's patient population when aggregated. We attempted to ensure this representativeness by enrolling patients and doctors from all over Japan and using stratified sampling in the elderly (65+) group to ensure the age and sex ratios would closely approximate corresponding estimates for the general population. Our strategy seems validated by the close concordance between our observed PPSV23 coverage (31.9% among adults 65+) and past data published by Japan's Ministry of Health, Labor and Welfare (33.5% and 37.8% among eligible adults in 2015 and in 2016, respectively).[22] Thus, it seems safe to assume that the rates calculated for our survey population essentially reflect the real coverage among Japan's elderly population nationwide. Finally, an inherent weakness of internet surveys is that they rely on self-reporting, calling into question the reliability of our data on respondents' medical conditions and vaccine type (PPSV23 vs. PCV13) and timing. We carefully and specifically designed our question items to maximize reliability, for example by explaining in detail the

setting of routine and voluntary vaccination. However, our investigation was undoubtedly hampered by poor memory on the part of respondents, as indicated by the large proportion who could not identify which vaccine they had received, as well as insufficient vaccine-related information. The real PPSV23 coverage in this demographic may be higher than estimated in this study.

In summary, our study reports PPSV23 vaccination rates in Japanese patients with CMC aged 50 and older for the first time, along with identifying factors that encourage patients to get it and reasons why doctors avoid it. Pneumonia risk is known to increase once adults reach the age of 50; however, information about benefit of pneumococcal vaccines does not currently seem to be well conveyed to those patients under 65 years at present. Clinicians have critical role to play in educating their patients population about their risk of pneumococcal disease to improve pneumococcal vaccine uptake. Although this survey might not indicate the situation in all over Japan, PPSV23 coverage would be increased by ensuring those patients eligible for PPSV23 under the routine immunization schedule know they are eligible and pursue vaccination, in addition to financial subsidies from local governments. These steps would go a long way toward protecting populations at high risk of pneumococcal infection. We urge municipal authorities to take proactive measures for the sake of patients with CMC.

Conclusion

PPSV23 has very low coverage among Japanese adults aged 50–64 with CMC. Doctors and local authorities need to raise public awareness to improve the vaccination rate, given the high risk of pneumococcal infection among patients with CMC.

Disclosure of potential conflicts of interest

In conjunction with the external investigators, this study was designed, executed, and analysed 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 from MSD K.K. AS, AW, TI are employees of MSD K.K., Tokyo, Japan, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. TF is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Employees may hold stock and/or stock options in Merck & Co., Inc., Kenilworth, NJ, USA.

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