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BRIEF REPORT

Protective Effects of 23-Valent Pneumococcal Polysaccharide Vaccination Against Mortality: The VENUS Study

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This retrospective matched cohort study investigated the protective effects of the 23-valent pneumococcal polysaccharide vaccine (PPSV23) against pneumonia mortality and all-cause mortality in Japanese adults aged ≥65 years. We analyzed claims data, vaccination records, and death certificate records between October 2016 and December 2019 from 55 509 PPSV23-vaccinated individuals and 55 509 unvaccinated individuals. Cox proportional hazards analyses were performed to calculate the adjusted hazard ratios (HRs) of PPSV23 vaccination for mortality. The results showed that PPSV23 vaccination was significantly associated with a reduction in all-cause mortality (adjusted HR, 0.52; $P < .001$) but not pneumonia mortality (adjusted HR, 0.70; $P = .374$).

Keywords. mortality; pneumonia; PPSV23; vaccine; real-world data.

The primary causative agent of pneumonia in adults is *Streptococcus pneumoniae* [1]. A study of 10 Japanese hospitals conducted in 2010 reported that *S pneumoniae* accounted for 17.1% of community-acquired pneumonia cases [2]. *S pneumoniae* can also migrate into normally sterile sites, resulting in invasive pneumococcal disease. In Japan, the mortality rate for cases of invasive pneumococcal disease between April 2013 and March 2017 was 19%, and 69% of patients were aged ≥65 years [3]. Given that pneumonia was the fourth-leading cause of death in the Japanese population in 2022 [4], the prevention of pneumococcal infection is an important health priority.

The US Centers for Disease Control and Prevention recommends immunization with the 23-valent pneumococcal polysaccharide vaccine (PPSV23) for persons aged ≥65 years and other high-risk groups to prevent pneumococcal infection [5]. In Japan, the Immunization Act was revised in October 2014 to include PPSV23 as a partially subsidized routine immunization for persons aged ≥65 years. Non-PPSV23 pneumococcal vaccines are not currently included in Japan's routine immunization program. However, the evidence on PPSV23's protective effects against mortality remains controversial. While some studies have found that PPSV23 vaccination significantly reduces pneumonia mortality and all-cause mortality [6, 7], others have found no such impact [8]. To our knowledge, there have been no studies on the protective effects of PPSV23 vaccination against pneumonia mortality and all-cause mortality in Japan. This study was conducted to examine these effects in Japanese adults aged ≥65 years.

METHODS

Study Design and Setting

This retrospective matched cohort study was conducted with claims data from the Longevity Improvement & Fair Evidence (LIFE) Study; vaccination records from the Vaccine Effectiveness, Networking, and Universal Safety (VENUS) Study; and death certificate records from the vital statistics published by the Ministry of Health, Labour and Welfare. The LIFE Study is a multiregional database project administered by Kyushu University (Fukuoka, Japan), which collects claims data from National Health Insurance enrollees and Latter-Stage Older Persons Health Care System enrollees for the purpose of research [9]. National Health Insurance is a public medical insurance scheme that covers persons not employed in companies (eg, primary sector workers, self-employed persons) and their dependents aged ≤74 years. The Latter-Stage Older Persons Health Care System is a public medical insurance scheme that covers residents aged 65 to 74 years with specific disabilities and all residents aged ≥75 years. These claims data include recorded diagnoses and medical procedures for all insurance-covered health care encounters. Vaccination records were obtained from the VENUS Study [10], which was created as a subproject of the LIFE Study to investigate vaccine effectiveness and safety in Japan. As such, the VENUS Study collects and merges vaccination records (vaccine types, vaccination dates, doses, manufacturers, and lot numbers) with the LIFE Study's data. The Ministry of Health, Labour and Welfare's vital statistics are derived from national surveys conducted to

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ascertain vital events and provide the basis for population and administrative policies [11]. These vital statistics include death certificate records that contain the birth dates, addresses, and death dates of residents who have died. For this study, we used the claims data, vaccination records, and death certificate records from 2 municipalities. The study period was from October 2016 to December 2019.

Since October 2014, Japanese residents aged ≥65 years are eligible to receive PPSV23 under partial municipal subsidy at specific 5-year increments (65, 70, 75, 80, 85, 90, 95, and 100 years). If individuals wish to receive PPSV23 outside of these specified ages (eg, at age 68 years), they can do so at their own expense. Our study population comprised older persons of these vaccine-eligible ages during the study period. As subsidies vary among the municipalities, vaccine recipients pay different copayments for PPSV23 vaccination (4000 yen and 1500 yen after subsidization in the 2 target municipalities).

Participants were assigned to a vaccinated group or unvaccinated group based on their PPSV23 vaccination status, as identified from the vaccination records. In this study, the effectiveness of PPSV23 was assumed to be constant over the study period. Each vaccinated participant's vaccination date was set as one's cohort entry date (CED). Next, each vaccinated participant was sequentially matched without replacement to an unvaccinated participant based on sex, age (in years), and municipality at the former's CED. The unvaccinated participants used the same CEDs as their vaccinated counterparts. The following were excluded from analysis: (1) individuals who were not enrolled in the National Health Insurance or Latter-Stage Older Persons Health Care System 6 months before their CEDs and (2) individuals who were hospitalized at the time of their CEDs.

Outcome Measures

The primary outcome measure was pneumonia mortality after the CED. The Japanese government publishes mortality statistics in the "Statistical Classification of Diseases, Injuries and Deaths," based on codes from the World Health Organization's *International Classification of Diseases, Tenth Revision* (*ICD-10*). We defined pneumonia mortality as cases in which the cause of death was allocated *ICD-10* codes J12 to J18. The secondary outcome measure was all-cause mortality after the CED.

Covariates

To account for variations in participant characteristics, we examined sex, age, comorbidities, and medical expenditures using the claims data. Age was analyzed as categories (65, 70, 75, 80, 85, 90, 95, and 100 years). For comorbidities, we identified the following Charlson Comorbidity Index conditions recorded in the 6 months before each participant's CED: myocardial infarction (*ICD-10* codes I21, I22, I25.2), congestive heart failure (I50), peripheral vascular disease (I71, I739, I790, R02, Z958, Z959), cerebrovascular disease (I60–I69, G450–G452, G454, G458, G459, G46), dementia (F00–F02, F051), chronic pulmonary disease (J40–J47, J61–J67), rheumatic disease (M32–M35, M058–M60, M063, M069), peptic ulcer disease (K25–28), mild liver disease (K702, K703, K717, K73, K740, K742–K746), diabetes without chronic complication (E101, E105, E109, E111, E115, E119, E131, E135, E139, E141, E145, E149), diabetes with chronic complication (E102–E104, E112–E114, E132–E134, E142–E144), hemiplegia or paraplegia (G041, G81–G822), renal disease (N01, N03, N052–N056, N072, N18–N19, N25), any malignancy (C0-C96), moderate or severe liver disease (K721, K729, K766, K767), metastatic solid tumor (C77–C80), and HIV/AIDS (B20–B24). For medical expenditures, we calculated the expenditures incurred during the 6 months before each participant's CED.

Statistical Analysis

First, we conducted a descriptive analysis in which continuous variables were analyzed as means (SD) and categorical variables were analyzed as percentages. The balance of covariates between the groups was assessed with a standardized mean difference threshold <0.1.

To analyze the impact of PPSV23 vaccination on pneumonia mortality, we constructed Cox proportional hazards models in which the dependent variable was the duration from the CED until pneumonia-related death and the independent variable of interest was PPSV23 vaccination (reference: unvaccinated). Sex, age category, comorbidities, and medical expenditures were included as covariates. The CED was set as the baseline, and observations were censored upon withdrawal from the target insurance schemes or moving out of the target municipalities, death, or end of the study period, whichever was earliest. Similar Cox proportional hazards models were constructed for the secondary outcome, with the dependent variable set as the duration from the CED until all-cause death. The models were used to estimate hazard ratios (HRs). Statistical analyses were performed with Stata version 17.0 (Stata Corp), and significance was set at $P < .05$.

RESULTS

The characteristics of the study participants are summarized in Table 1. The study population consisted of 55 509 participants vaccinated with PPSV23 matched with an equal number of unvaccinated participants. Women constituted 62.9% of each group, and 70-year-olds were the most represented age category (29.9%). The most prevalent comorbidity in both groups was diabetes without chronic complication (unvaccinated, 27.3%; vaccinated, 28.5%). The mean (SD) medical expenditures in the 6 months before the CED were 137 852 yen (370 032) in the unvaccinated group and 117 564 yen (305 061) in the

Table 1. Characteristics of the Study Participants According to PPSV23 Vaccination Status

	Unvaccinated (n = 55 509)	Vaccinated (n = 55 509)	Standardized Difference
Female	34 932 (62.9)	34 932 (62.9)	…
Age category, y			…
65	8227 (14.8)	8227 (14.8)	
70	16 600 (29.9)	16 600 (29.9)	
75	12 635 (22.7)	12 635 (22.7)	
80	9151 (16.5)	9151 (16.5)	
85	5663 (10.2)	5663 (10.2)	
90	2412 (4.3)	2412 (4.3)	
95	718 (1.3)	718 (1.3)	
100	103 (0.2)	103 (0.2)	
Comorbidities[a]			
Myocardial infarction	1175 (2.1)	1005 (1.8)	0.02
Congestive heart failure	9132 (16.5)	9181 (16.5)	−0.00
Peripheral vascular disease	5903 (10.6)	6391 (11.5)	−0.03
Cerebrovascular disease	9178 (16.5)	9300 (16.8)	−0.00
Dementia	3010 (5.4)	2768 (5.0)	0.02
Chronic pulmonary disease	9899 (17.8)	10 938 (19.7)	−0.05
Rheumatic disease	2078 (3.7)	2029 (3.7)	0.00
Peptic ulcer disease	8677 (15.6)	9380 (16.9)	−0.03
Mild liver disease	9339 (16.8)	10 286 (18.5)	−0.04
Diabetes without chronic complication	15 175 (27.3)	15 828 (28.5)	−0.03
Diabetes with chronic complication	3361 (6.1)	3128 (5.6)	0.02
Hemiplegia/paraplegia	467 (0.8)	362 (0.7)	0.02
Renal disease	2257 (4.1)	2009 (3.6)	0.02
Any malignancy	6677 (12.0)	6616 (11.9)	0.00
Moderate/severe liver disease	198 (0.4)	159 (0.3)	0.01
Metastatic solid tumor	865 (1.6)	646 (1.2)	0.03
HIV/AIDS	12 (0.02)	12 (0.02)	0.00
Medical expenditures (yen), mean [SD][a]	137 852 [370 032]	117 564 [305 061]	0.06
Pneumonia mortality	16 (0.03)	11 (0.02)	…
All-cause mortality	544 (1.0)	256 (0.5)	…

Values are presented as No. (%) unless otherwise indicated.

Abbreviation: PPSV23, 23-valent pneumococcal polysaccharide vaccine.

[a]During the 6 months before each participant's cohort entry date.

Table 2. Cox Proportional Hazards Analyses of the Associations Between PPSV23 Vaccination and Mortality

	Unadjusted		Adjusted	
Mortality	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Pneumonia	0.68 (.32–1.47)	.332	0.70 (.33–1.52)	.374
All cause	0.47 (.40–.54)	<.001	0.52 (.45–.61)	<.001

HRs were calculated for PPSV23 vaccination with "unvaccinated" as the reference. Cox regression analyses adjusted for participant sex, age, comorbidities, and medical expenditures in the previous year.

Abbreviations: HR, hazard ratio; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

vaccinated group. Pneumonia mortality was 0.03% in the unvaccinated group and 0.02% in the vaccinated group. All-cause mortality was 1.0% in the unvaccinated group and 0.5% in the vaccinated group. The standardized mean differences between the groups were <0.1 for all variables.

Table 2 shows the results of the Cox proportional hazards analyses of the associations between PPSV23 vaccination and mortality. PPSV23 vaccination was not significantly associated with pneumonia mortality (adjusted HR, 0.70; $P = .374$). However, the PPSV23 group had a significantly lower hazard for all-cause mortality than the unvaccinated group (adjusted HR, 0.52; $P < .001$).

DISCUSSION

With claims data, vaccination records, and death certificate records from >110 000 individuals from 2 Japanese municipalities, this study evaluated the protective effects of PPSV23 vaccination against pneumonia mortality and all-cause mortality. While PPSV23 vaccination showed a numerically lower hazard for pneumonia mortality, this association was not statistically significant. This result may have been influenced by the low incidence of pneumonia deaths in our study population. In contrast, PPSV23-vaccinated participants had a significantly lower hazard for all-cause mortality than unvaccinated participants. These findings are similar to those of a previous study

from Spain that reported a lower, but not significant, incidence of pneumonia deaths following PPSV23 vaccination [8]. That study examined persons aged ≥60 years from the general population and concluded that PPSV23 vaccination did not reduce the risk of pneumonia mortality.

Our analysis showed that PPSV23 vaccination significantly reduced the risk of all-cause mortality. A previous study reported that PPSV23 vaccination was associated with significantly lower odds of acute myocardial infarction and stroke events in older persons [12]. The vaccine-associated reduction of these events may have contributed to the lower risk of all-cause mortality, but not pneumonia mortality, in our cohort.

This study has several limitations. First, the analyses were conducted with data from public medical insurance enrollees in 2 municipalities. As a result, the findings have limited generalizability. Second, vaccination status was determined from records of subsidized immunizations. As a designated routine immunization, PPSV23 vaccination is partially subsidized by each municipality. Nevertheless, some individuals may have chosen to receive the PPSV23 vaccine or another pneumococcal vaccine at their own expense. Therefore, the unvaccinated group may include some self-funded vaccinated persons. Third, our study data did not include records on influenza vaccination, which may have affected pneumonia incidence. Fourth, we could not identify the types of pneumonia in cases of pneumonia mortality. Finally, mean medical expenditures were higher in the unvaccinated group, suggesting that this group may contain more unaccounted health conditions that might explain the difference in overall mortality.

Despite these limitations, this study provides important insight into the impact of PPSV23 vaccination on pneumonia mortality and all-cause mortality in a Japanese population. The PPSV23 vaccination rate has remained low in Japan and was only 14% in 2021 [13]. Increasing the subsidies for PPSV23 could help to improve vaccination coverage, which may contribute to the reduction of pneumonia, invasive pneumococcal disease, and all-cause mortality.

CONCLUSION

PPSV23 was associated with reduced all-cause mortality in our cohort. Further studies are needed to explore this relationship in larger populations and other regions.

Notes

Author contributions. F. M., M. M., and H. F. designed the study and collected the data. F. M. performed the analysis, and all authors interpreted the results. F. M. drafted the original manuscript. All authors reviewed and edited the manuscript. The study was supervised by H. F. All authors read the manuscript and approved its submission for publication.

Patient consent statement. The study was approved by the Kyushu University Institutional Review Board for Clinical Research (No. 22114-01). Based on Japanese ethical guidelines, the requirement for individual informed consent was waived, as this secondary analysis was conducted using anonymized data routinely collected by the municipalities.

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