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Effectiveness of 23-valent pneumococcal polysaccharide vaccine and seasonal influenza vaccine for pneumonia among the elderly – Selection of controls in a case-control study

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ABSTRACT

We conducted a case-control study to elucidate associations between pneumonia in elderly individuals and 23-valent pneumococcal polysaccharide vaccine (PPSV23) and seasonal influenza vaccine (influenza vaccine). Here, we examined selection of controls in our study using an analytic epidemiology approach. The study period was from October 1, 2009 through September 30, 2014. Cases comprised ≥65-year-old patients newly diagnosed with pneumonia. For every case with pneumonia, two patients with other diseases (one respiratory medicine, one non-respiratory medicine) who were sex-, age-, visit date- and visit hospital-matched were selected as controls. Odds ratios (ORs) and 95% confidence intervals (CIs) of vaccination for pneumonia were calculated using conditional logistic regression model. Similar analyses were also conducted based on the clinical department of controls. Analysis was conducted in 234 cases and 438 controls. Effectiveness of pneumococcal vaccination or influenza vaccination against pneumonia was not detected. Proportions of either vaccination in controls were greater among respiratory medicine (pneumococcal vaccine, 38%; influenza vaccine, 55%) than among non-respiratory medicine (23%; 48%). Analysis using controls restricted to respiratory medicine showed marginally significant effectiveness of pneumococcal vaccination (OR, 0.59; 95%CI, 0.34–1.03; P = 0.064) and influenza vaccination (0.64; 0.40–1.04; 0.072). However, this effectiveness might have been overestimated by selection bias of controls, as pneumonia cases are not necessarily respiratory medicine patients. In the analysis using controls restricted to non-respiratory medicine, OR of pneumococcal vaccination for pneumonia was close to 1, presumably because the proportion of pneumococcal vaccination was higher in cases than in controls. Because pneumococcal vaccine was not routinely administered during the study period, differences in recommendations of vaccination by physician in different clinical departments might have greatly affected vaccination proportions. When we select controls, we should consider the background factors (underlying diseases, clinical department, etc.) which affect physicians' recommendation of vaccination.

1. Introduction

Pneumonia is the third leading cause of death in Japan, and the mortality rate by age group is high in the elderly, particularly among individuals ≥80 years old [1]. With Japanese society aging at an unprecedented rate not seen anywhere else in the world, prevention of pneumonia among the elderly is becoming a critical issue. In our country, both pneumococcal vaccine and seasonal influenza vaccine (influenza vaccine) have been recommended.

Abbreviations: PPSV23, 23-valent pneumococcal polysaccharide vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; influenzavaccine, seasonal influenza vaccine; COPD, chronic obstructive pulmonary disease; ADL, activities of daily living; OR, odds ratio; CI, confidence interval.

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For adults aged 65 years or older, 23-valent pneumococcal polysaccharide vaccine (PPSV23) can be provided as a periodical inoculation (starting from October 1, 2014) through the national vaccination program and 13-valent pneumococcal conjugate vaccine (PCV13) can be inoculated as arbitrary vaccination [2]. On the other hand, the Advisory Committee on Immunization Practices (ACIP) in the United States recommended PPSV23 and PCV13 for adults 65 years old or older in September 2014 [3].

Large-scale observational studies from the United States, Sweden, and Hong Kong have investigated the association between pneumonia in the elderly and influenza and/or pneumococcal vaccinations, and have demonstrated that vaccinations have decreased hospitalizations and deaths caused by influenza or pneumonia [4–7]. A Japanese study of nursing home residents showed that PPSV23 prevented pneumococcal pneumonia and thus reduced mortality from pneumococcal pneumonia [8]. Kawakami et al. reported the effectiveness of the PPSV23 against pneumonia in elderly people 75 years old or older who received the influenza vaccine in Japan [9]. We conducted a case-control study from October 1, 2009 to September 30, 2014 to investigate the effects of pneumococcal and influenza vaccines on pneumonia prevention among elderly individuals in Japan. If our study covered four vaccination patterns (no inoculation with either vaccine, inoculation with influenza vaccine only, inoculation with PPSV23 only, inoculation with both vaccines), we thought that we might be able to clarify the effectiveness of each vaccination pattern.

Selecting appropriate controls is extremely important in a case-control study. Controls must be selected from the population to which the cases belong, but vaccine effectiveness studies must also consider whether both cases and controls have had the opportunity to be exposed to the pathogen (necessary cause). The present study considered the opportunity for exposure to the pathogen to be relatively uniform within an area, and therefore controls were defined as hospital controls. In addition, because pneumococcal vaccine was not routinely administered during our study period, the recommendation of vaccinations by physician may be different in various clinical departments. We therefore further selected controls from non-respiratory medicine.

Here, we examined the selection of controls in our case-control study on the basis of an analytical epidemiology approach, and discussed the methods for investigating vaccine effectiveness in the elderly.

2. Material and methods

2.1. Study subjects

A hospital-based matched case-control study at 24 hospitals in Tokyo, Chiba, Shizuoka, Aichi, Gifu, Kyoto, and Fukuoka was conducted between October 1, 2009 and September 30, 2014. Because the study outcome was community-acquired pneumonia (CAP), study subjects were limited to outpatients (i.e., those living in their own home or in a home for the elderly that resembled their own home). All study participants received an explanation of the study content and provided consent prior to participation. The study protocol was approved by the Ethics Committee at the Osaka City University Graduate School of Medicine and was conducted in accordance with the principles of the Helsinki Declaration.

Cases were ≥65-year-old patients who were newly diagnosed with pneumonia by a physician. Pneumonia was diagnosed based on increased white blood cell count or elevated levels of C-reactive protein (CRP), and the presence of an infiltrative shadow on chest X-rays in addition to clinical presentation (cough, sputum, fever).

Controls were sex-, age (grouped in 5-year increments)-, visit date- (within 2 months after visit by case)-, and visit hospital-matched patients without pneumonia. As much as possible, two controls (one respiratory medicine and one non-respiratory medicine) were selected for each case.

Exclusion criteria were: presence of aspiration pneumonia; presence of malignant tumor; current treatment with oral steroid or immunosuppressant; and history of splenectomy.

2.2. Data collection

The attending physicians of cases and controls completed a questionnaire that included the following clinical information: a) sex, age, presence or absence of underlying respiratory system disease (pulmonary emphysema, chronic bronchitis, diffuse panbronchiolitis, pulmonary fibrosis, bronchial asthma, pulmonary tuberculosis sequelae); and b) disease information related to pneumonia (cases only), comprising date of definitive diagnosis and test results concerning pathogenic diagnosis (influenza rapid diagnostic test, pneumococcal urinary antigen test, sputum Gram staining, sputum culture, blood culture).

Cases and controls completed a self-administered questionnaire that included the following information: presence or absence of underlying disease (respiratory system disease, hypertension, hypercholesterolemia, heart disease, cerebral hemorrhage, cerebral infarction, stroke, diabetes mellitus, kidney disease), activities of daily living (ADL) (bedridden, semi-bedridden, semi-self-supported, self-supported), and vaccination status (23-valent pneumococcal polysaccharide vaccine (PPSV23), monovalent influenza A (H1N1) pdm09, trivalent seasonal influenza vaccine (influenza vaccine)).

2.3. Statistical analysis

Subjects who had received the pneumococcal vaccine within the past 5 years were considered "vaccinated," while all others were considered "unvaccinated." Subjects who had received the influenza vaccine (monovalent influenza A (H1N1) pdm09 vaccine, trivalent seasonal influenza vaccine) within the past 6 months were considered "vaccinated," while all others were considered "unvaccinated." All underlying diseases were analyzed as "present vs. absent" and ADL were analyzed as "non-self-supported (bedridden, semi-bedridden, semi-self-supported) vs. self-supported." For medical institutions that did not have a respiratory medicine, clinical department was determined based on the condition of the subject at the time of the visit: visits for respiratory system diseases were considered "respiratory medicine," and visits for all other diseases were considered "non-respiratory medicine."

The Wilcoxon rank-sum test and the chi-square test were used where appropriate to compare characteristics between cases and controls.

The odds ratio (OR) and 95% confidence interval (CI) of vaccination for pneumonia were calculated using a conditional logistic regression model. Variables included in the multivariate analysis model were pneumococcal vaccination, influenza vaccination, respiratory system disease, hypertension, diabetes mellitus, and ADL.

Next, to investigate the effects by different clinical departments, similar analyses were conducted based on the clinical department (respiratory medicine or non-respiratory medicine) of the control subjects. Variables included in each multivariate model were similar to those of the overall multivariate model. However, respiratory system diseases were excluded in the model using controls restricted to respiratory medicine.

Values of $P < 0.05$ were considered statistically significant. SAS software (version 9.3, SAS Institute, Cary, NC) was used for analysis. Since the influenza A (H1N1) pandemic occurred and seasonal

influenza did not spread during the 2009–2010 season [10], monovalent influenza A (H1N1) pdm09 vaccine was considered as the influenza vaccine.

3. Results

A total of 234 cases and 438 controls were enrolled. Table 1 shows the comparison of characteristics between cases and controls. The proportion of pneumococcal vaccination was 27% in cases and 30% in controls, and the proportion of influenza vaccination was 44% in cases and 51% in controls. The prevalence of hypertension and diabetes mellitus in controls was significantly greater than cases. The proportion of self-supported participants in controls was significantly greater than cases. Significant differences between cases and controls were not observed in any other variables. Among our cases, 24% (56 of 234 cases) represented pneumococcal pneumonia. Test results concerning the pathogenic diagnosis of cases were as follows: 24% (46 of 190 cases) showed positive results to the pneumococcal urinary antigen test, *Streptococcus pneumoniae* was detected by sputum Gram staining in 23% (28 of 124 cases), *S. pneumoniae* was detected by sputum culture in 22% (33 of 147 cases), and *S. pneumoniae* was detected by blood culture in 57% (4 of 7 cases).

Table 2 shows the OR of vaccination for pneumonia in all study subjects. The crude OR of pneumococcal vaccination was 0.90 (95% CI: 0.60–1.35, $P = 0.603$), and the adjusted OR decreased to 0.84 (95%CI: 0.54–1.30, P = 0.437). The crude OR of influenza vaccination was 0.71 (95%CI: 0.50–1.03, $P = 0.070$), and the adjusted OR was 0.74 (95%CI: 0.51–1.08, $P = 0.119$).

Results of analysis by the clinical departments of controls are shown in Table 3. When controls were restricted to respiratory medicine, there were 188 cases and 208 respiratory medicine controls for analysis (155 sets of case: respiratory medicine control: non-respiratory medicine control = 1:1:1; 13 sets of case: respiratory medicine control: non-respiratory medicine control = 1:1:0; and 20 sets of case: respiratory medicine control: non-respiratory medicine control = 1:2:0). The adjusted OR of pneumococcal vaccination for pneumonia was 0.59 (95%CI: 0.34–1.03, P = 0.064) and the adjusted OR of influenza vaccination for pneumonia was 0.64 (95%CI: 0.40–1.04, P = 0.072), with both vaccines showing marginal significance. Among respiratory medicine controls, the pneumococcal vaccination proportion was 38% and the influenza vaccination proportion was 55%.

When controls were restricted to non-respiratory medicine, 201 cases and 230 non-respiratory medicine controls were analyzed (155 sets of case: respiratory medicine control: non-respiratory medicine control = 1:1:1; 17 sets of case: respiratory medicine control: non-respiratory medicine control = 1:0:1; and 29 sets of case: respiratory medicine control: non-respiratory medicine control = 1:0:2). The adjusted OR of pneumococcal vaccination for pneumonia was 0.98 (95%CI: 0.49–1.95, P = 0.949) and the adjusted OR of influenza vaccination for pneumonia was 0.68 (95%CI: 0.39–1.17, P = 0.163). In non-respiratory medicine controls, the pneumococcal vaccination proportion was 23% and the influenza vaccination proportion was 48%.

Table 1
Characteristics of cases and controls.

Characteristics	Cases (n = 234)	Controls (n = 438)	*P*
Age (mean years, range)	77.2 (65–99)	76.8 (65–100)	0.518[b]
Sex			
Male	148 (63)	279 (64)	0.908[c]
Female	86 (37)	159 (36)	
Pneumococcal vaccine			
Unvaccinated	170 (73)	307 (70)	0.486[c]
Vaccinated	64 (27)	131 (30)	
Influenza vaccine			
Unvaccinated	131 (56)	213 (49)	0.069[c]
Vaccinated	103 (44)	225 (51)	
Underlying disease			
Respiratory system disease[a]	96 (41)	176 (40)	0.832[c]
Hypertension	106 (45)	237 (54)	0.030[c]
Hypercholesterolemia	32 (14)	80 (18)	0.128[c]
Heart disease	40 (17)	88 (20)	0.346[c]
Cerebral hemorrhage, cerebral infarction, stroke	27 (12)	38 (9)	0.232[c]
Diabetes mellitus	32 (14)	105 (24)	0.002[c]
Kidney disease	7 (3)	18 (4)	0.466[c]
ADL			
Self-supported	179 (76)	378 (86)	0.001[c]
Semi-self-supported, semi-bedridden, or bedridden	55 (24)	60 (14)	

Variables are expressed as number (percent), unless otherwise specified.
[a] Pulmonary emphysema, chronic bronchitis, diffuse panbronchiolitis, pulmonary fibrosis, bronchial asthma, pulmonary tuberculosis sequelae.
[b] Wilcoxon rank-sum test.
[c] Chi-square test.

4. Discussion

In the present study, analysis using controls restricted to respiratory medicine showed marginal effectiveness of the pneumococcal vaccine. However, vaccine effectiveness in the examination using controls restricted to respiratory medicine might be overestimated by selection bias of controls, because pneumonia cases are not necessarily respiratory medicine patients. On the other hand, analysis using controls restricted to non-respiratory medicine showed that the OR of pneumococcal vaccination for pneumonia was approximately 1. This is because the proportion of pneumococcal vaccination among cases (27%) was higher than proportion of pneumococcal vaccination among non-respiratory medicine controls (23%).

The rate of pneumococcal vaccination in Japan during the study period has been estimated at around 20%, although this number is not absolute due to large differences based on region and clinical department. The proportion of pneumococcal vaccination in the present study differed greatly depending on the clinical department, and was significantly higher among respiratory medicine controls (38%) than among non-respiratory medicine controls (23%). We expected that the extent of recommendations of vaccination by physician would have been different depending on the clinical department because the pneumococcal vaccine was not routinely administered during the study period. According to the above-mentioned result, when we perform case-control study under the situation that pneumococcal vaccine is not routinely administered, we should select controls in consideration of the background factors (clinical section, underlying disease) which affect physicians' recommendation of pneumococcal vaccination.

The mean rate of influenza vaccination during the study period in Japan was 51% [11]. The proportion of influenza vaccination in the present study was 55% in respiratory medicine controls and 48% in non-respiratory medicine controls. Because the influenza vaccine was routinely administered, the influenza vaccination proportion among non-respiratory medicine patients resembled that in the general population. Therefore, in case-control studies of routinely administered influenza vaccine, selection of controls from non-respiratory medicine might also be necessary, on the basis of the theory that controls must be selected from the population to which the cases belong.

When we examine vaccine effectiveness in case-control studies in situations where a vaccine is not routinely administered, controls should be selected in consideration of the background factors

Table 2
Odds ratios of vaccination (pneumococcal vaccine and influenza vaccine) for pneumonia.

	Cases (n = 234) n (%)	Controls (n = 438) n (%)	Crude OR	95%CI	*P*	Adjusted OR[a]	95%CI	*P*
Pneumococcal vaccine								
Unvaccinated	170 (73)	307 (70)	1			1		
Vaccinated	64 (27)	131 (30)	0.90	0.60–1.35	0.603	0.84	0.54–1.30	0.437
Influenza vaccine								
Unvaccinated	131 (56)	213 (49)	1			1		
Vaccinated	103 (44)	225 (51)	0.71	0.50–1.03	0.070	0.74	0.51–1.08	0.119

[a] Model included pneumococcal vaccination, influenza vaccination, underlying respiratory system disease, hypertension, diabetes mellitus and ADL.

Table 3
Vaccination proportion of pneumococcal vaccine and influenza vaccine and odds ratios of vaccination for pneumonia (by clinical departments of Controls).

Object for analysis	n/n	Pneumococcal vaccination				Influenza vaccination			
		Proportion (%)	Adjusted OR[a]	95%CI	*P*	Proportion (%)	Adjusted OR[a]	95%CI	P
All cases/all controls	234/438	27/30	0.84	0.54–1.30	0.437	44/51	0.74	0.51–1.08	0.119
All cases/respiratory medicine controls	188/208	29/38	0.59	0.34–1.03	0.064	45/55	0.64	0.40–1.04	0.072
All cases/non-respiratory medicine controls	201/230	27/23	0.98	0.49–1.95	0.949	43/48	0.68	0.39–1.17	0.163

[a] Model included the same as Table 2, but underlying respiratory system disease was excluded in "All cases/respiratory medicine controls".

affecting physician recommendations for vaccination. On the other hand, in situations where a vaccine is routinely administered, selection of controls from various clinical departments appears desirable.

We discussed the selection of controls in this case-control study on the basis of an analytical epidemiological approach, but some limitations must be acknowledged in this study. We included aspiration pneumonia as an exclusion criterion. In the planning stages of the current study in 2008, aspiration pneumonia (i.e., pneumonia associated with physical factors such as aspiration at the time of eating) was excluded because we thought that its mechanism was different from "normal" pneumonia. However, it later became clear that the incidence of aspiration pneumonia determined according to swallowing function testing was high among hospitalized patients with CAP and HAP [12]. Therefore, use of aspiration pneumonia as an exclusion criterion might be inappropriate. A further limitation was that we obtained information about vaccination status from a patient questionnaire, but were unable to verify the validity of that information.

Conflict of interest statement

The authors have no competing interests to declare.

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Appendix

The other members of the Pneumonia in Elderly People Study Group are listed with their affiliation: Noriko Kojimahara (Tokyo Women's Medical University); Sakae Kan (Kaisei Hospital); Chiharu Ota, Ikuji Usami, Munehiro Kato, Toshinobu Yamamoto (Asahi Rosai Hospital); Kazuhide Yamamoto (Kazu Clinic); Yoichi Nakanishi, Takanari Kitazono (Graduate School of Medical Sciences, Kyushu University); Nobumitsu Fujisawa, Takafumi Matsumoto, Hideki Tashiro (St. Mary's Hospital); Masahiko Taketomi (Doukai Clinic); Tomoaki Iwanaga, Hiroko Nogami (Fukuoka National Hospital); Koichi Takano (Nishifukuoka Hospital); Ken Tonegawa, (Nagoya City Koseiin Geriatric Hospital); Yoshimitsu Hayashi (Kasugai Municipal Hospital); Seiichiro Imai (Graduate School of Medicine, Kyoto University); Ikuo Ikeda (Ikeda Clinic); Shigeki Sugiyama (Sugiyama Clinic); Kunihiko Yoshimura (Mitsui Memorial Hospital), Masahiro Aoshima, Kei Nakashima (Kameda Medical Center), Yoshitaka Nakamori, Yasushi Seida, Yoshiko Kichikawa (Mishuku Hospital), Akira Adachi (Kasadera Hospital), Atsushi Nakamura (Graduate School of Medical Sciences, Nagoya City University), Yasuhito Iwashima (Iwashima Clinic), Yasuhiro Kojima (Kojima Clinic), Yasuo Yamada (Yama Clinic), Hidekazu Kawamura (Kawamura Clinic), Toshiaki Niwa (Hamada Asai Clinic), Atsuro Kawai (Kawai Clinic), Yuuji Ito, Emi Aoyama (Daiyukai Hospital), Noriko Kusada, Chizuko Sumida (Inazawa Municipal Hospital), Naoyuki Miyashita (Department of Internal Medicine 1, Kawasaki Medical School).

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