

# Association between monovalent influenza A (H1N1) pdm09 vaccine and pneumonia among the elderly in the 2009–2010 season in Japan: A case-control study

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**Keywords:** effectiveness, elderly people, matched case-control study, monovalent influenza A (H1N1) pdm09 vaccine, pneumonia

**Abbreviations:** H1N1pdm, monovalent influenza A (H1N1) pdm09; TIV, trivalent seasonal influenza vaccine; COPD, chronic obstructive pulmonary disease; ADL, activities of daily living; OR, odds ratio; CI, confidence interval.

We investigated the association between monovalent influenza A (H1N1) pdm09 (H1N1pdm) vaccine and pneumonia in elderly people. Study design was a hospital-based, matched case-control study. Cases comprised patients  $\geq 65$  years old who had been newly diagnosed with pneumonia. For each case, 2 controls were defined as individuals with other diseases (not pneumonia) who were matched by sex, age, entry date, and the visited hospital. Study period was the interval from 1 September 2009 until 30 September 2010. Because a pandemic of influenza A (H1N1) occurred during study period, we analyzed selected subjects who had enrolled during the influenza A (H1N1) pandemic. We calculated the odds ratios (ORs) and 95% confidence intervals (CIs) for pneumonia in H1N1pdm-vaccinated subjects compared with unvaccinated subjects using a conditional logistic regression model to assess the association between H1N1pdm vaccine and pneumonia. The subjects during the period of the influenza A (H1N1) pandemic were 20 cases and 40 controls. Subjects who had received H1N1pdm vaccine showed a significantly decreased OR for pneumonia (OR = 0.10, 95% CI = 0.01–0.98) compared with unvaccinated subjects. In conclusion, H1N1pdm vaccination may have prevented pneumonia among the elderly during the 2009–2010 influenza A (H1N1) pandemic in Japan.

## Introduction

Pneumonia is the third largest cause of death in Japan. The death rate increases with age group, and particularly high rate (more than 1,100 per a population of 100,000 people in 2007) are observed among individuals  $\geq 80$  y old.<sup>1</sup> With Japanese society aging at a rate not seen anywhere else in the world, prevention of pneumonia is becoming a major challenge in this country. Many studies have reported preventive relationships between influenza vaccination and hospitalization due to pneumonia or influenza among elderly people.<sup>2–7</sup> On the other hand, Jackson et al. reported that influenza vaccination was not associated with a reduced risk of community-acquired pneumonia after adjusting

for the presence and severity of comorbidities.<sup>8</sup> Variations in the results of different studies reflect several confounding variables, definitions of influenza seasons, and mismatches between vaccine strains and those circulating in the community.

Few studies in Japan have examined the association between influenza vaccine and pneumonia among the elderly. Therefore we conducted a hospital-based, matched case-control study between September 2009 and September 2010 to elucidate the effectiveness of influenza vaccination in preventing pneumonia among the elderly. Due to a pandemic of influenza A (H1N1) that occurred in Japan during our study period,<sup>9</sup> a monovalent influenza A (H1N1) pdm09 (H1N1pdm) vaccination program was initiated in the last 10 d of October 2009. Although a

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**Table 1.** Characteristics of cases and controls during the 2009 influenza A(H1N1) pandemic

Characteristics*	Cases (N = 20)	Controls (N = 40)	P value
Age (mean years, range)	79.8 (65 – 95)	79.4 (65 – 97)	0.832 <sup>†</sup>
Male	11 (55)	22 (55)	1.000 <sup>‡</sup>
H1N1pdm vaccinated	4 (20)	14 (35)	0.232 <sup>‡</sup>
Pneumococcal vaccine vaccinated	7 (35)	9 (22)	0.302 <sup>‡</sup>
Underlying respiratory system disease	11 (55)	15 (37)	0.197 <sup>‡</sup>
Underlying disease			
Hypertension	10 (50)	21 (53)	0.855 <sup>‡</sup>
Hypercholesterolemia	2 (10)	3 (8)	1.000 <sup>§</sup>
Heart disease	6 (30)	13 (33)	0.844 <sup>‡</sup>
Cerebral hemorrhage, Cerebral infarction, Stroke	3 (15)	5 (13)	1.000 <sup>§</sup>
Diabetes mellitus	2 (10)	8 (20)	0.471 <sup>§</sup>
Kidney disease	0 (0)	2 (5)	0.548 <sup>§</sup>
Smoking (past or current)	8 (40)	18 (45)	0.713 <sup>‡</sup>
ADL			
Self-support	10 (50)	29 (73)	0.085 <sup>‡</sup>
Others (semi-self-support, semi-bedridden, or bedridden)	10 (50)	11 (27)	

ADL: activities of daily living, H1N1pdm: monovalent influenza A (H1N1) pdm09.

\*Variables are expressed as number (percent), unless otherwise specified.

† Wilcoxon rank-sum test, ‡ Chi-square test, § Fisher exact test.

trivalent seasonal influenza vaccine (TIV) vaccination program was initiated in October 2009, a seasonal epidemic did not occur.<sup>9</sup> Hence we investigate here the association between H1N1pdm vaccine and pneumonia in elderly people.

## Results

During the influenza A (H1N1) pandemic, subjects totaled 20 cases and 40 controls from 7 medical institutions in Aichi, Kyoto, and Fukuoka.

**Table 1** shows a comparison of characteristics of cases and controls. The proportion of H1N1pdm vaccination (in the preceding 6 months), pneumococcal vaccination (in the preceding 5 years), underlying respiratory system disease,

hypertension, hypercholesterolemia, heart disease, cerebral hemorrhage, cerebral infarction, stroke, diabetes mellitus, kidney disease, smoking, and ADL status were not significantly different between cases and controls. In our study population, 94% of the subjects who received H1N1pdm vaccine also received TIV (17/18 subjects).

**Table 2** shows the association between H1N1pdm vaccination and pneumonia among the elderly during the influenza A (H1N1) pandemic itself. Subjects who received H1N1pdm vaccine showed a significantly decreased adjusted OR for pneumonia (0.10, 95% CI = 0.01–0.98) compared with unvaccinated subjects. Pneumococcal vaccination and underlying respiratory system disease were not associated with pneumonia. The odds ratio for pneumonia increased significantly among subjects with low ADL status.

**Table 2.** Association between H1N1pdm vaccine and pneumonia among the elderly during the 2009 influenza A(H1N1) pandemic<sup>†</sup>

	Cases n (%)	Controls n (%)	Crude OR	95%CI	P	Adjusted OR <sup>‡</sup>	95%CI	P
H1N1pdm vaccine								
Unvaccinated	16 (80)	26 (65)	1			1		
Vaccinated	4 (20)	14 (35)	0.37	0.09–1.54	0.171	0.10	0.01–0.98	0.048
Pneumococcal vaccine								
Unvaccinated	13 (65)	31 (78)	1			1		
Vaccinated	7 (35)	9 (22)	2.35	0.55–10.0	0.249	3.46	0.50–24.1	0.209
Underlying respiratory system disease								
No	9 (45)	25 (63)	1			1		
Yes	11 (55)	15 (37)	1.80	0.66–4.89	0.248	3.65	0.76–17.4	0.105
ADL								
Self support	10 (50)	29 (73)	1			1		
Others (semi-self-support, semi-bedridden, or bedridden)	10 (50)	11 (27)	10.0	1.17–85.6	0.036	23.8	1.91–296	0.014

†The influenza A (H1N1) pandemic was defined as the weeks during which there were ≥10 reports of influenza cases reported by the sentinels in the prefectures covered by the study (see main text).

‡Model included H1N1pdm vaccination, pneumococcal vaccination, underlying respiratory system disease, and ADL.

H1N1pdm: monovalent influenza A (H1N1) pdm09, OR: odds ratio, CI: confidence interval, ADL: activities of daily living.

## Discussion

In this study, the OR for pneumonia in subjects with H1N1pdm vaccination decreased significantly among elderly people during the period of the influenza A (H1N1) pandemic. Some researchers have reported that influenza vaccination reduces hospitalization due to pneumonia or influenza among elderly people living in the community.<sup>3-6</sup> In the 2009–2010 season, both vaccination against H1N1pdm and seasonal vaccination<sup>2</sup> and vaccination against MF59- adjuvant H1N1pdm<sup>7</sup> showed the preventive effect of influenza and pneumonia in elderly persons. Our decreased odds ratio for pneumonia suggests that during the period of the influenza A (H1N1) pandemic, H1N1pdm vaccination was associated with prevention of influenza A (H1N1) and reduction of the incidence of secondary pneumonia accompanying influenza. On the one hand, our results did not demonstrate efficacy for pneumococcal vaccination. Specifically, pneumococcal pneumonia was diagnosed in only 2 of the 20 pneumonia cases that we observed during the period of the influenza A (H1N1) pandemic, suggesting that our cases consisted predominantly of other (non-pneumococcal) pneumonias.

The presence of confounding factors is a difficult problem in studies of influenza vaccine effectiveness in the elderly.<sup>10</sup> Old age, underlying respiratory system disease, hypertension, hypercholesterolemia, heart disease, cerebral hemorrhage, cerebral infarction, stroke, diabetes mellitus, kidney disease, smoking, and low ADL status are associated with an increased risk of hospitalization due to pneumonia or influenza.<sup>11</sup> On the other hand, the vaccination rate typically is higher in healthy elderly than in weak elderly. *Pneumococcus* is cited as the major pathogenic bacterium in community-acquired pneumonia in the Japanese,<sup>12</sup> and the 23-valent pneumococcal polysaccharide vaccine has reduced the prevalence of pneumococcal pneumonia.<sup>13</sup> We matched controls with case patients by sex, age, entry date, and hospital, and investigated underlying respiratory system disease, hypertension, hypercholesterolemia, heart disease, cerebral hemorrhage, cerebral infarction, stroke, diabetes mellitus, kidney disease, smoking, ADL status, and pneumococcal vaccination status. The proportions of these variables were not significantly different between cases and controls. So, in multivariate model, we included underlying respiratory system disease, ADL status, and pneumococcal vaccination status that were important pathophysiological variables whether statistically significant or insignificant. Furthermore, because we did not detect an association between pneumococcal vaccination status and pneumonia, we calculated the OR adjusted for underlying respiratory disease and ADL status. The directionality of the result did not change (data not shown). We note, however, that even with adjustment for confounders, a selection bias still might have been present in the evaluation of the effectiveness of the influenza vaccine.<sup>14</sup>

We obtained information about vaccination status from each patient's questionnaire, but we were not able to confirm the validity of this information; this point represents a weakness of

this study. Cases are expected to claim lack of vaccination more frequently than controls would, a pattern that would represent a possible information bias in our study. However, H1N1pdm vaccine non-inoculation was reported by 80% of cases and 65% of controls; pneumococcal vaccine non-inoculation was reported by 65% of cases and 78% of controls. Thus, self-reported H1N1pdm vaccine non-inoculation frequency was higher in cases than in controls, but the reverse was seen for pneumococcal vaccine non-inoculation. Therefore, information bias is considered unlikely in the context of our study.

In our study population, TIV inoculation was reported in 94% (17/18 subjects) of H1N1pdm vaccine inoculators; TIV non-inoculation was reported in 88% (37/42 subjects) of H1N1pdm vaccine non-inoculators. In other words, we considered that it was inappropriate to include TIV vaccination as an adjustment factor because of the near perfect correlation between TIV vaccination and H1N1pdm vaccination.

A smaller immune response was observed in subjects who had received the 2009–2010 seasonal influenza vaccine prior to H1N1pdm vaccination.<sup>15</sup> Because 94% of our study subjects were inoculated with both vaccines, we could not evaluate the effect of this factor. However, even if antibody production was reduced in response to the H1N1pdm vaccination, vaccination efficacy would have been underestimated, and so this factor would not have affected the validity of our study.

We showed significantly increased OR for pneumonia even when we adjusted for vaccination and the presence of an underlying respiratory disease in subjects with low ADL status. Fever occurred more frequently in those requiring higher care levels, and the main cause of such fevers was pneumonia.<sup>16</sup> Our study suggested that ADL levels would have been associated with pneumonia in the elderly.

One of the weaknesses of our study is that our matched entry date might lead to a bias. In our protocol, we enrolled controls as soon as a possible (within about 2 months) after the respective case had been enrolled. This difference in entry date between cases and controls might have given the controls more time to become vaccinated. However, controls were enrolled (on average) 10 d later than the respective case's entry; in only one instance was the control enrolled about a full 2 months after the case's entry. Therefore we do not expect that the entry dates lead to a bias.

We managed to increase the statistical power of our study by providing 2 controls for each pneumonia patient. Nevertheless, the greatest limitation of the present study was that the number of subjects was small. In practice, our 95% confidence interval was 0.01–0.98. Therefore, it would be inappropriate to calculate vaccine efficacy from our point estimate level after adjustment. However, we think that it was noteworthy that significant association was detected between H1N1pdm vaccination status and pneumonia despite the small size of our study. We expect that our study will provide a valuable data source, because our study period spanned the season in which the influenza A (H1N1) pandemic occurred. We are engaged in ongoing research to investigate the effectiveness of a seasonal influenza vaccine against pneumonia among the elderly.

## Materials and Methods

### Study design

We performed a hospital-based, matched case-control study in 7 hospitals (in the prefectures of Aichi, Kyoto, and Fukuoka) between September 2009 and September 2010. All subjects provided informed consent after the nature of the study had been explained. The study protocol was approved by the ethics committee at the Osaka City University Graduate School of Medicine and was performed in accordance with the Declaration of Helsinki.

### Definition of cases and controls

Cases comprised patients  $\geq 65$  y old who had been newly diagnosed with pneumonia by a doctor at one of the 7 medical institutions cooperating with the study. A pneumonia diagnosis was based on clinical symptoms (cough, sputum, or fever), increased white blood cell counts or serum C-reactive protein level, and the appearance of an infiltrate on a chest radiograph at the hospitals or the clinics of the study investigators.<sup>17</sup>

For each case, 2 controls were selected from individuals with other diseases (not pneumonia) who were matched by sex, age (in 5-year age groups), entry date (soon after a given case's entry, within about 2 months), and the visited hospital.

Exclusion criteria were aspiration pneumonia, malignant tumor, ongoing treatment with oral corticosteroids or immunosuppressant drugs, and previous splenectomy.

### Data collection

The physicians of each case or control completed a structured questionnaire regarding the following clinical information: (a) sex, age, presence of underlying respiratory system disease (pulmonary emphysema, chronic bronchitis, other chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, bronchial asthma, pulmonary tuberculosis sequelae, etc.); and (b) information relating to pneumonia (for cases): date of definite diagnosis, and test results relating to cause of pneumonia (rapid diagnosis test of influenza, detection of urinary pneumococcal antigen, Gram staining of sputum, sputum or blood culture).

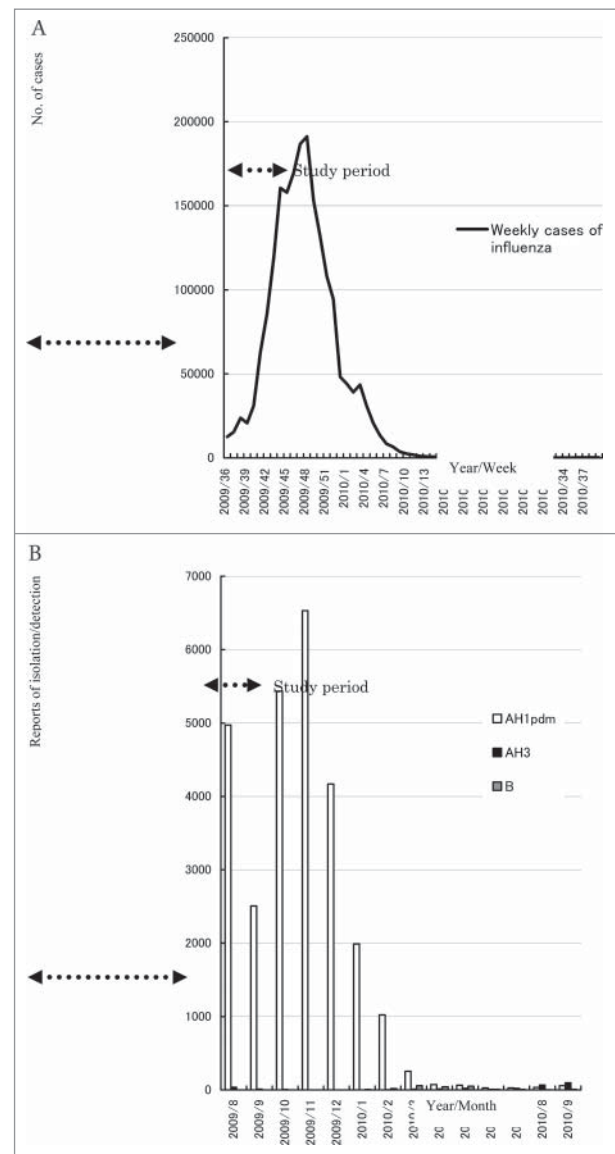
Each case or control completed a self-administered questionnaire regarding the following information: presence of underlying respiratory system disease, hypertension, hypercholesterolemia, heart disease, cerebral hemorrhage, cerebral infarction, stroke, diabetes mellitus, kidney disease, smoking (never, past, or current), activities of daily living (ADL: bedridden, semi-bedridden, semi-self-support, self-support), pneumococcal vaccination (in the last 5 years), TIV vaccination (in the last 6 months), and H1N1pdm vaccination (in the last 6 months).

The H1N1pdm strain was A/California/7/2009. The 2009–2010 TIV strains were A/Brisbane/59/2007 (H1N1), A/Urugay/716/2007 (H3N2), and B/Brisbane/60/2008.

### Period of survey and influenza A (H1N1) pandemic

This study was initiated on 1 September 2009. We defined study period as the interval from initiation until 30 September

2010, because the vaccination program for the 2010–2011 season started on 1 October 2010. During the study period, a pandemic of influenza A (H1N1) occurred. Thus we analyzed selected subjects who had enrolled during the influenza A (H1N1) pandemic. The influenza A (H1N1) pandemic was defined as those weeks during which  $\geq 10$  influenza cases were reported by the sentinels in the prefectures covered by the study, based on data from the Infectious Disease Weekly Report and the Infectious Agents Surveillance Report. The periods meeting this definition were as follows: the period from the 38th week of 2009 until the 5th week of 2010 (between 14 September 2009 and 7 February 2010) in Aichi; the period from the 36th week of 2009 until the 3rd week of 2010



**Figure 1.** (A) Study period and weekly cases of influenza in Japan from week 35 of 2009 to week 39 of 2010. (B) Study period and monthly reports of isolation/detection of influenza viruses in Japan from August 2009 to September 2010.



(between 31 August 2009 and 24 January 2010) in Kyoto; and the period from the 35th week of 2009 until the 6th week of 2010 (between 24 August 2009 and 14 February 2010) in Fukuoka.<sup>9</sup> **Figure 1A** provides the study period and plotting the numbers of weekly cases of influenza in Japan from week 35 of 2009 to week 39 of 2010. **Figure 1B** provides the study period and the numbers of monthly reports of isolation/detection of influenza viruses in Japan from August 2009 to September 2010.<sup>9</sup> A seasonal epidemic did not occur in the prefectures covered by the study.

### Statistical analysis

Characteristics of cases and controls were compared using a Wilcoxon rank-sum test and  $\chi^2$  test, as appropriate.

We calculated the odds ratios (ORs) and 95% confidence intervals (CIs) for pneumonia in H1N1pdm-vaccinated subjects compared with those in unvaccinated subjects using a conditional logistic regression model.

We adjusted for pneumococcal vaccination (yes in the last 5 years, no), underlying respiratory system disease (yes, no), and ADL (other (bedridden, semi-bedridden, or semi-self-support), self-support) in multivariate analyses.

The significance level for statistical analysis was set at  $P < 0.05$ . Analyses were performed using SAS version 9.3 software (SAS Institute, Cary, NC, USA).

## Conclusions

We conducted a hospital-based, matched case-control study between September 2009 and September 2010 to elucidate the association between influenza vaccine and pneumonia in elderly people. Our results indicate that H1N1pdm vaccination may have prevented pneumonia among the elderly during the 2009–2010 influenza A (H1N1) pandemic in Japan

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### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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### Authors' Contributions

KK designed the study, did the statistical analysis, interpreted the results and wrote the first draft of the article. KS and MW designed the study, collected data, interpreted the results, and edited drafts of the article. SO, WF, AM and YH designed the study, interpreted the results and edited drafts of the article. Members of the Pneumonia in Elderly People Study Group (Note) collected data and interpreted the results. All authors read and approved the final draft of the article.

### Note

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