Original Study

Prevention of Mortality and Pneumonia Among Nursing Home Older Adults by Dual Pneumococcal and Seasonal Influenza Vaccination During a Pandemic Caused by Novel Pandemic Influenza A (H1N1)

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A B S T R A C T

Objective: To evaluate the efficacy of dual vaccination of seasonal influenza and pneumococcus in nursing home older adults during a novel pandemic of influenza A (H1N1).

Setting: Nine nursing homes in Hong Kong.

Participants: A total of 532 nursing home older adults were included in the study.

Measurements: Efficacy of dual vaccination of seasonal influenza and pneumococcus in nursing home older adults during a novel pandemic influenza A (H1N1).

Design: A prospective 12-month cohort study was conducted on older residents from December 2009 to November 2010. Participants were divided into 3 groups according to their choice of vaccination: received both seasonal influenza and 23-valent pneumococcal polysaccharide vaccine (PPV-TIV group), received seasonal influenza vaccine alone (TIV group), and those who refused both vaccinations (unvaccinated group). Those who had received vaccination for influenza A (H1N1) were excluded.

Outcome measures included mortality from all causes, pneumonia, and vascular causes.

Results: There were 246 in the PPV-TIV group, 211 in the TIV group, and 75 in the unvaccinated group. Baseline characteristics were similar among the groups. The 12-month mortality rates of the PPV-TIV, TIV alone group, and unvaccinated group were 17.1%, 27.0%, and 37.3% respectively (P < .001). Multivariate analysis demonstrated that, compared with vaccination of seasonal influenza alone, dual vaccination significantly reduced all-cause mortality (hazard ratio [HR] 0.54; 95% confidence interval [CI]: 0.35–0.84; P < .01), mortality from pneumonia (HR 0.60; 95% CI: 0.35–0.99; P < .05), and mortality from vascular causes (HR 0.24; 95% CI: 0.09–0.64; P < .01).

Conclusions: During an influenza pandemic or when the circulating influenza strain was not matched by the trivalent seasonal influenza vaccine, dual vaccination of influenza and pneumococcus provided additional protection to nursing home older adults in reducing mortality.

Pneumonia is the third leading cause of death in Hong Kong.1 Influenza viruses and Streptococcus pneumoniae are 2 major causes of pneumonia.2–4 Nursing home older adults is a major at-risk population.5,6 Annual seasonal influenza vaccination for the older adults and at-risk populations has always been covered by the Hong Kong government and the program usually begins in November every year. Uptake of seasonal influenza vaccination is high in nursing home older adults. On the other hand, uptake of pneumococcal vaccination in older adults in Hong Kong was low before 2009, as it was not included in the government vaccination program. In view of local evidence that pneumococcal vaccination may be able to cover 85% of strains and reduce pneumococcal pneumonia and its related complications, a free pneumococcal vaccination program for older adults and at-risk populations was launched in Hong Kong in 2009.7–9 In June 2009, the World Health Organization declared the novel strain of swine-origin influenza A (H1N1) 2009 as pandemic. In Hong
Kong, this novel influenza virus contributed to significant hospitalization and mortality. The H1N1 2009 attack rate in Hong Kong was 10.7% during the first wave up to December 2009. In laboratory surveillance of detected influenza virus by the Centre of Health Protection, more than 90% of viruses isolated were H1N1 2009 in October 2009. Case hospitalization rate was nearly 1%. Older adults (those older than 50 years) had 66 times higher risks of mortality if they became infected. A mass vaccination program for the (H1N1) 2009 was launched in December 2009, which was shown to reduce mortality in nursing home older adults. However, fewer than 3% of the Hong Kong population and fewer than 40% of nursing home older adults were vaccinated because of fear of potential adverse effects.

A recent prospective study on dual pneumococcal and influenza vaccination on the local population demonstrated its benefit in prevention of respiratory, cardiovascular, and cerebrovascular complications in the community-based elderly population. However, the impact of dual vaccination in nursing home older adults during an influenza pandemic has never been studied before. We therefore performed a prospective cohort study to assess the efficacy of dual pneumococcal and influenza vaccination during an influenza pandemic.

Methods

Study Design

We performed a prospective cohort study to assess the efficacy of dual vaccination of the 23-valent pneumococcal vaccine (PPV) and trivalent seasonal influenza vaccine (TIV) in nursing home older adults on mortality, from December 2009 to November 2010. All patients gave informed consent for the vaccines they received. The study was approved by the institutional review boards at the University of Hong Kong and Hospital Authority.

Study Sites and Participants

The study was performed in the Hong Kong West Cluster (HKWC), 1 of the 7 major health districts in Hong Kong under the Hospital Authority, which provides public hospital service for all Hong Kong citizens. In 2009, the population of HKWC was 530,000, and there were more than 70 nursing homes taking care of more than 6000 older adults.

The Department of Health of Hong Kong provides an annual vaccination program for older adults living in nursing homes. The seasonal influenza vaccination program and the first free pneumococcal vaccination program were started in November 2009. The TIV used was trivalent influenza vaccine containing 15 μg hemagglutinin of the following strain: an A/Brisbane/59/2007 (H1N1)-like virus, an A/Brisbane/10/2007 (H3N2)-like virus, and a B/Brisbane/60/2008-like virus. The PPV used was 23-valent Pneumovax (Sanofi Pasteur MSD; Lyon, France).

The quality of care and facility of the nursing home may affect vaccination acceptance, epidemic transmission of infective diseases, and hospitalization. To minimize the selection bias, 9 nursing homes were included. They were all operated by charitable nonprofit organizations and they had a standardized caregiver to older adults ratio and facility to provide comparable quality of care.

The inclusion criteria were adults aged 65 or older, living in 1 of the 9 nursing homes. Participants were divided into 3 groups according to their choice of vaccination. The first group was older adults who consented to have both TIV and PPV (PPV-TIV group), the second group was older adults who consented to have TIV only (TIV group), and the third group was older adults who refused both vaccinations (unvaccinated group). During the same period of study, the vaccination program for pandemic influenza A (H1N1) was carried out in November 2009, but fewer than 3% of the Hong Kong population was vaccinated because of fear of potential adverse effects. Those who received the vaccination were excluded.

Data Collection

Vaccination status for seasonal influenza, pneumococcus, and pandemic influenza A (H1N1) were collected from patient records of nursing homes. Prior history of pneumococcal vaccination for residents during their stay in the nursing home was also retrieved from patient records. Nursing homes have a record of the vaccination status of each resident, even if the resident was vaccinated in the private sector.

Baseline demographic data, including age, gender, smoking history, number of medications, and feeding status (oral feeding or nonoral feeding, eg, percutaneous endoscopic gastrostomy) had been collected through the computer management system (CMS) and patient consultation records. The CMS has records of comorbidity on the basis of The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). CMS also has a record of patient demographics, any hospitalization, medication use, laboratory results, and death for all patients registered in the system. The nursing home where the patient lived was recorded and regarded as “the nursing home of origin.”

The numbers and types of comorbidities were quantified using the Charlson Co-morbidity index (CCI). The CCI was first introduced in 1987, with each comorbidity factor assigned with a score depending on the risk of dying associated with this condition. It is valid and reliable to measure comorbidity that can be used in clinical research. Functional status of subjects was assessed by the Barthel Index 20 (BI[20]). The BI[20] is a validated functional scale that measures performance in basic activities of daily living. It has 10 variables describing activities of daily living and mobility; a higher score indicates better functional status and it is regarded as reliable for measuring the functional status of patients.

Older adults with multiple comorbidities and functional decline often require hospitalization in their last few years of life, leading to further functional decline and morbidity. Frequency of hospitalization in the past year may represent a key trigger point for identifying older adults at higher risk of mortality, so the number of nonscheduled hospitalizations documented in the CMS between December 2008 and November 2009 were recorded as “hospitalization in preceding year.”

The clinical status of patients was monitored half-yearly from November 2009 to November 2010 by retrieving patient records and CMS. Mortality of patients and cause(s) of death were studied. Outcomes were all-cause mortality, mortality attributable to pneumonia based on the ICD-9-CM, and mortality attributable to any vascular cause based on the ICD-9-CM.

Statistics

The Statistical Package for the Social Sciences (Windows version 18; SPSS Inc, Chicago, IL) was used in statistical analysis. Continuous variables were expressed as either mean ± SD if they were normally distributed or median with the interquartile range if their distribution is skewed. Independent t test was used to compare the change of continuous variables of 2 different groups. Analysis of variance (ANOVA) was used to compare the change of continuous variables for 3 different groups if the variables were normally distributed. The Kruskal-Wallis test was used to compare the change of continuous variables for 3 different groups if the distribution of variables was skewed. The chi-square test and Fisher’s exact test were used to compare categorical variables. The effectiveness of the vaccine in the
prevention of mortality was estimated using multivariable Cox proportional hazard models, which we adjusted for covariates. Age, gender, smoking status, number of medications and feeding status, CCI, BI(20), nursing home of origin, hospitalization in preceding year, and vaccination status for pneumococcus and seasonal influenza were considered as covariates. Kaplan-Meier curves were constructed to illustrate the cumulative rate of mortality between groups during the 12-month follow-up. Statistical significance was inferred by a 2-tailed *P* value of .05 or less.

**Results**

A total of 532 nursing home older adults were included in the study; 246 of them belonged to the PPV-TIV group, 211 to the TIV group, and 75 to the unvaccinated group. None of them received prior pneumococcal vaccination after living in nursing homes. There was no significant difference among the 3 groups for age, gender, smoking status, feeding status, number of medications, CCI, BI(20), or hospitalization in preceding year (Table 1).

### All-Cause Mortality

At 12 months of study, 17.1% (42 of 246) of the PPV-TIV group, 27.0% (57 of 211) of the TIV group, and 37.3% (28 of 75) of the unvaccinated group died. Comparison by log rank test showed there was a significant difference (*P* < .001) (Figure 1).

Between the PPV-TIV group and TIV group, multivariate analysis using Cox proportional hazard models by entering age, gender, smoking status, nursing home of origin, CCI, and BI as covariates showed the hazard ratio for the PPV-TIV group was 0.54 (95% confidence interval [CI], 0.35–0.86; *P* < .001). The PPV-TIV group had a 66% reduction in all-cause mortality compared with the TIV group. Between the PPV-TIV group and the unvaccinated group, multivariate analysis showed the hazard ratio was 0.34 (95% CI, 0.21–0.54; *P* < .001). The PPV-TIV group had a 66% reduction in all-cause mortality compared with the unvaccinated group. Between the TIV group and the unvaccinated group, multivariate analysis showed the hazard ratio was 0.66 (95% CI, 0.42–1.02; *P* = .06), but it was not statistically significant.

### Mortality Attributable to Pneumonia Based on ICD-9-CM

At 12 months of study, excluding censored cases who died from other causes, 11.7% (27 of 231) of the PPV-TIV group, 20.2% (39 of 193) of the TIV group, and 24.2% (15 of 62) of the unvaccinated group died of pneumonia based on the ICD-9-CM (*P* < .05) (Figure 2).

Between the PPV-TIV group and the TIV group, multivariate analysis showed the hazard ratio for the PPV-TIV group was 0.60 (95% CI, 0.35–0.99; *P* < .05). The PPV-TIV group had a 40% reduction in mortality attributable to pneumonia compared with the TIV group. Between the PPV-TIV group and the unvaccinated group, multivariate analysis showed the hazard ratio was 0.45 (95% CI, 0.24–0.86; *P* < .05). The PPV-TIV group had a 55% reduction in mortality attributable to pneumonia compared with the unvaccinated group. Between the TIV group and the unvaccinated group, multivariate analysis showed the hazard ratio was 0.82 (95% CI, 0.45–1.53; *P* = .54), but it was not statistically significant.

### Table 1

<table>
<thead>
<tr>
<th>Baseline Characteristics of Subjects</th>
<th>PPV-TIV Group (n = 246)</th>
<th>TIV-Alone Group (n = 211)</th>
<th>Unvaccinated Group (n = 75)</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>85.7 ± 7.6</td>
<td>86.0 ± 8.0</td>
<td>85.1 ± 8.9</td>
<td>.72</td>
</tr>
<tr>
<td><strong>Sex (female), %</strong></td>
<td>60.2</td>
<td>65.6</td>
<td>54.3</td>
<td>.23</td>
</tr>
<tr>
<td><strong>Smoking status (ex-smoker &amp; smoker), %</strong></td>
<td>17.1</td>
<td>15.6</td>
<td>14.7</td>
<td>.45</td>
</tr>
<tr>
<td><strong>Feeding status, nonoral</strong></td>
<td>6.9</td>
<td>6.6</td>
<td>10.7</td>
<td>.12</td>
</tr>
<tr>
<td><strong>No. of medications</strong></td>
<td>3.2 ± 1.6</td>
<td>3.6 ± 1.7</td>
<td>4.0 ± 1.8</td>
<td>.11</td>
</tr>
<tr>
<td><strong>Hospitalization in preceding year</strong></td>
<td>1 (0–2)</td>
<td>1 (0–2)</td>
<td>1 (0–3)</td>
<td>.74</td>
</tr>
<tr>
<td><strong>Charlson Comorbidity Index</strong></td>
<td>2.8 ± 1.5</td>
<td>2.8 ± 1.5</td>
<td>2.59 ± 1.46</td>
<td>.41</td>
</tr>
<tr>
<td><strong>Ischemic heart disease, %</strong></td>
<td>21.1</td>
<td>16.3</td>
<td>13.9</td>
<td>.17</td>
</tr>
<tr>
<td><strong>Chronic pulmonary disease, %</strong></td>
<td>10.2</td>
<td>12.7</td>
<td>12.0</td>
<td>.68</td>
</tr>
<tr>
<td><strong>Chronic liver disease, %</strong></td>
<td>0.4</td>
<td>0.5</td>
<td>1.3</td>
<td>.63</td>
</tr>
<tr>
<td><strong>Congestive heart failure, %</strong></td>
<td>17.1</td>
<td>15.6</td>
<td>13.3</td>
<td>.73</td>
</tr>
<tr>
<td><strong>Diabetes, %</strong></td>
<td>28.2</td>
<td>27.4</td>
<td>24.0</td>
<td>.77</td>
</tr>
<tr>
<td><strong>Peripheral vascular disease, %</strong></td>
<td>4.5</td>
<td>2.4</td>
<td>2.7</td>
<td>.43</td>
</tr>
<tr>
<td><strong>Dementia, %</strong></td>
<td>72.0</td>
<td>75.0</td>
<td>73.3</td>
<td>.76</td>
</tr>
<tr>
<td><strong>Cerebrovascular disease, %</strong></td>
<td>39.0</td>
<td>38.7</td>
<td>29.3</td>
<td>.29</td>
</tr>
<tr>
<td><strong>Chronic renal impairment, %</strong></td>
<td>7.3</td>
<td>10.8</td>
<td>9.3</td>
<td>.42</td>
</tr>
<tr>
<td><strong>Barthel Index 20</strong></td>
<td>4 (1–15)</td>
<td>4 (1–12)</td>
<td>4 (1–11)</td>
<td>.71</td>
</tr>
</tbody>
</table>

Data are mean ± SD. Analysis of variance was used for continuous variables if variables were normally distributed and Kruskal-Wallis test was used for continuous variables if the distribution of variables was skewed. Chi-square test was used for categorical variable.
Between the PPV-TIV group and the unvaccinated group, multivariate analysis showed the hazard ratio was 0.24 (95% CI, 0.09–0.64; \( P < .01 \)). The PPV-TIV group had a 76% reduction in mortality attributable to any vascular cause compared with the unvaccinated group. Between the PPV-TIV group and the TIV group, multivariate analysis showed the hazard ratio for the PPV-TIV group was 0.47 (95% CI, 0.16–1.41; \( P = .18 \)), but it was not statistically significant. Between the TIV group and the unvaccinated group, multivariate analysis showed the hazard ratio was 0.42 (95% CI, 0.17–1.06; \( P = .06 \)), but it was not statistically significant.

**Discussion**

This study suggested that for nursing home older adults who did not receive vaccination of pandemic influenza A (H1N1), dual vaccination of seasonal influenza and pneumococcus was more effective than the influenza vaccination alone. It significantly reduced all-cause mortality, mortality attributable to pneumonia, and mortality attributable to vascular causes. This is similar to the findings in our previous study in the community-based elderly population.\(^7\)

Efficacy of pneumococcal vaccination in older adults is a debated topic because of conflicting evidence. There were studies suggesting that pneumococcal vaccination was effective in reducing mortality or hospitalization.\(^{23–25}\) It was cost-effective to make it a mass vaccination program;\(^{26}\) nevertheless, some prospective studies had opposite findings.\(^{27–29}\) Similar conflicting evidence about efficacy was also found in the dual vaccination of pneumococcus and influenza.\(^{22,30}\)

The major difference between this study and other studies was the presence of a pandemic influenza during the study period and the very low vaccination rate toward this pandemic influenza in Hong Kong. In laboratory surveillance of detected influenza virus by the Centre of Health Protection, more than 90% of viruses isolated were (H1N1) 2009 in December 2009. Fewer than 3% of the Hong Kong population was vaccinated for pandemic (H1N1) because of fear of potential adverse effects.\(^{12,13}\) Vaccination of the monovalent pandemic (H1N1) can induce a satisfactory immunological response and reduce mortality in older adults.\(^{13,31}\) For those who did not receive vaccination for the pandemic (H1N1), vaccination of the seasonal influenza alone obviously was a mismatch. As a result, they had a higher chance of being infected by the pandemic (H1N1) and subsequent secondary pneumococcal pneumonia. Those who received both the pneumococcal and seasonal influenza vaccines were protected against secondary pneumococcal infection even when there was a mismatch in the influenza vaccine strain. We concluded that pneumococcal vaccination is particularly important when there is a mismatch between the prevalent influenza strain and that covered by the trivalent seasonal influenza vaccine, or when there is emergence of a novel pandemic influenza, as pneumococcal vaccination becomes a second line to decrease mortality.

The finding of this study is a very important public health issue. Although the free pneumococcal vaccination program for older adults and at-risk populations was launched in Hong Kong in 2009, as demonstrated in this study, the vaccination rate for pneumococcus in nursing home older adults was low. It may be for reasons similar to the low vaccination rate on (H1N1) 2009, which was lack of confidence of the vaccine and worry of adverse effects. Other possible reasons included inadequate publicity of the program or inadequate information about the efficacy of the pneumococcal vaccine. The Centre of Health Protection of Hong Kong suggests anyone older than 65 years should receive the pneumococcal vaccination. There was still a significant proportion of institutionalized elderly who did not receive pneumococcal vaccination. The health authority should make more of an effort in promoting the free pneumococcal vaccination program and constantly remind elderly persons about the efficacy of
pneumococcal vaccination, especially during the influenza peak seasons.

Pneumococcal vaccines are perceived to offer low protection in frail older adults owing to hypoimmunogenicity toward it. However, the latest evidence suggested that although baseline antibody levels were slightly lower in the older age groups (especially in those who were frail), the first vaccination or revaccination of *Pneumococcus* retains immunogenicity when administered into the eighth decade of life. The finding in our study supported that the immune protection against *Pneumococcus* may be able to significantly reduce mortality.

One of the major strengths of this study was the involvement of functional status and comorbidity of older adults as covariates. The efficacy of any vaccination may commonly be overestimated because of fraility selection bias. Fraility selection bias means a subset of undervaccinated and frail elderly people have contributed to a substantial proportion of all deaths studied. Comorbidity is an important predictor for pneumococcal pneumonia that should be measured, but isolated assessment of it is inadequate for frail nursing home older adults. With involvement of frailty assessment by using hospitalization in the preceding year, functional assessment by using BI(20) and comorbidity assessment by using CCI, reduced the chance of overestimation of the efficacy of vaccine.

Our previous study on a community-based elderly population demonstrated that dual vaccination protects the elderly population against not only respiratory but also vascular complications. The result from this study supported this finding, which showed a decrease in mortality from vascular events in the PPV-TIV group compared with the unvaccinated group. Pneumococcal pneumonia was suggested to be associated with different vascular events owing to inflammatory stimulus. The effect is seen for a first or a subsequent myocardial infarction or stroke and is most marked in the first few days after infection. Pneumococcal vaccination was suggested to decrease atherosclerotic lesion formation because of antibodies directed against *Streptococcus pneumoniae* also recognize oxidized low-density lipoprotein (LDL) and impedes the formation of foam cells.

There were several limitations in this study. First, the participants were not randomized for ethical reasons; however, it may be unethical to withhold vaccination, the conflicting evidence of available studies justifies a prospective randomized study. Second, in terms of outcome measurement, we did not include laboratory-confirmed pneumococcal infection, which was direct evidence for pneumococcal infection. Third, although none of the participants had received prior pneumococcal vaccination after living in a nursing home, it was unknown whether they had received prior pneumococcal vaccination before living in the nursing home. The immunity against *Pneumococcus* may be different and might contribute to overestimation of vaccine efficacy. Fourth, although we tried to minimize frailty selection bias by including admission in the preceding year, functional assessment, and comorbidity measurement, the excessive mortality in the unvaccinated group (37%) compared with mortality of nursing home older adults measured in other local studies (5-year mortality of 60%), suggested our measurement of frailty may not be comprehensive. There may be other important confounding factors not being measured in this study. Moreover, the proportion of nonoral feeding and number of medications were more in the unvaccinated group, which suggested that these individuals may be frailer. The comparatively small sample size in the unvaccinated group may be the reason for the difference not being statistically significant. The sample size in the PPV-TIV group and the TIV group was larger, however. The mortality in these 2 groups was also comparable to the mortality measured in another local study. The final conclusion about the efficacy of pneumococcal vaccination during the period of pandemic influenza should not be affected. We suggest further study with a larger sample size after power analysis and involvement of more confounding factors to confirm the vaccine efficacy. Fifth, the sample included in this study was nursing home older adults. Compared with community-dwelling older adults, they are associated with more functional impairment, more comorbidities, and higher risk of unplanned readmission and 12-month mortality (>10% in studies for Hong Kong institutionalized older adults versus 4% in Hong Kong community-dwelling elderly). It prevented generalization of findings to older adults living in the community. Last, we collected the number of medications but the proportion of nursing home older adults taking certain types of medications, such as statins, was not collected, which may affect the estimation of vaccine efficacy.

**Conclusion**

This prospective cohort suggested that for nursing home older adults who did not receive vaccination for pandemic influenza A (H1N1), dual vaccination of the 23-valent pneumococcal vaccine and trivalent seasonal influenza vaccine significantly reduced all-cause mortality, mortality attributable to pneumonia, and mortality attributable to vascular causes, compared with vaccination of trivalent seasonal influenza vaccine alone during a pandemic period by pandemic influenza A (H1N1). It suggested that pneumococcal vaccination is particularly important when there is a mismatch between the strain of prevalent influenza and the strain covered by trivalent seasonal influenza vaccine or when there is a pandemic influenza, as pneumococcal vaccination becomes a second line to decrease mortality. The health authority should make further effort to inform the public of this finding to increase the vaccination rate for pneumococcus.

**References**

8. Luery KY, Kam KM. Vaccine coverage of *Streptococcus pneumoniae* in Hong Kong with attention to the multiple antibiotic resistant strains. Vaccine 1996;14:1573–1580.


