Prevention of Acute Myocardial Infarction and Stroke among Elderly Persons by Dual Pneumococcal and Influenza Vaccination: A Prospective Cohort Study

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(See the articles by Janjua et al, on pages 1017–1027, and by Liu et al, on pages 1028–1032.)

Background. Despite World Health Organization recommendations, the rate of 23-valent pneumococcal (PPV) and influenza (TIV) vaccination among elderly persons in Hong Kong, China, is exceptionally low because of doubts about effectiveness of vaccination. The efficacy of dual vaccination remains unknown.

Methods. From 3 December 2007 to 30 June 2008, we conducted a prospective cohort study by recruiting outpatients aged ≥65 years with chronic illness to participate in a PPV and TIV vaccination program. All were observed until 31 March 2009. The outcome of subjects, including the rates of death, hospitalization, pneumonia, ischemic stroke, acute myocardial infarction, and coronary and intensive care admissions, were determined.

Results. Of the 36,636 subjects recruited, 7292 received both PPV and TIV, 2076 received TIV vaccine alone, 1875 received PPV alone, and 25,393 were unvaccinated, with a duration of follow-up of 45,834 person-years. Baseline characteristics were well matched between the groups, except that there were fewer male patients in the PPV and TIV group and fewer cases of comorbid chronic obstructive pulmonary disease among unvaccinated persons. At week 64 from commencement of the study, dual-vaccinees experienced fewer deaths (hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.55–0.77; P < .001) and fewer cases of pneumonia (HR, 0.57; 95% CI, 0.51–0.64; P < .001), ischemic stroke (HR, 0.67; 95% CI, 0.54–0.83; P < .001), and acute myocardial infarction (HR, 0.52; 95% CI, 0.38–0.71; P < .001), compared with unvaccinated subjects. Dual vaccination resulted in fewer coronary (HR, 0.59; 95% CI, 0.44–0.79; P < .001) and intensive care admissions (HR, 0.45; 95% CI, 0.22–0.94; P = .03), compared with among unvaccinated subjects.

Conclusions. Dual vaccination with PPV and TIV is effective in protecting elderly persons with chronic illness from developing complications from respiratory, cardiovascular, and cerebrovascular diseases, thereby reducing hospitalization, coronary or intensive care admissions, and death.

Pneumococcal and influenza infections can cause serious morbidity and mortality, especially in the elderly population. In Hong Kong, overcrowded living conditions facilitate the transmission of both influenza and pneumococcal infection. Although a 23-valent pneumococcal polysaccharide vaccine (PPV) and a trivalent influenza vaccine (TIV) are available for prevention of pneumococcal and influenza infection respectively, the worldwide rates of uptake of these vaccines have been limited and variable [1–4]. There has been conflicting evidence on whether receipt of PPV can reduce the risk of community-acquired pneumonia and death among elderly persons, defined as those aged ≥65 years in most...
of the studies [5–9]. The evidence in favor of TIV for prevention of influenza and pneumonia in the elderly population appears to be more robust [10]. In addition, several large, prospective studies in Sweden and the United States have shown an additive beneficial effect of dual vaccination, with additional reductions in the risk of hospitalization for influenza or pneumonia and in death [11–13]. More interestingly, several studies and reviews have demonstrated that systemic respiratory infection can be associated with a transient increased risk of vascular events [14–18]. Therefore, we performed a large prospective cohort study to evaluate the impact of dual PPV and TIV vaccination, PPV or TIV vaccination alone, and no vaccination on mortality and on hospital and intensive care unit (ICU) admissions for pneumonia, coronary artery disease, and stroke.

METHODS

Study Design

All patients aged ≥65 years with chronic illness who attended the outpatient clinics in the Hong Kong West Cluster (HKWC), China, from 3 December 2007 through 30 June 2008 were enrolled in a prospective cohort study. During this period, participants were invited to receive PPV and TIV. All participants were observed until 31 March 2009.

Ethics Statement

This study was approved by the institutional review boards at the University of Hong Kong and Hospital Authority HKWC. Written informed consent was obtained for all participants receiving vaccination, and verbal informed consent was obtained for those participants who refused vaccination to be included in the study.

Study Sites and Participants

The study was conducted at the 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. The HKWC includes an acute care tertiary teaching hospital for the University of Hong Kong and 4 convalescent care hospitals. The HKWC provides hospital and outpatient care for an estimated population of 530,000 persons, of which 13% are aged ≥65 years. Participants were eligible if they were aged ≥65 years and had 1 of the following chronic illness: asthma, chronic obstructive pulmonary disease (COPD), coronary artery disease, hypertension, diabetes mellitus, stroke, chronic renal or liver disease, or malignancy. Patients with known allergy to eggs or other components of the study vaccines, those with immunosuppression as a result of underlying illness or treatment, those who had received anticancer chemotherapy or radiation therapy during the preceding 12 months, and HIV-infected patients were excluded. Before enrollment, all participants attended a video session on the potential benefits and adverse effects of the vaccines, with information leaflets provided. After vaccination, the patient’s name, Hong Kong resident identification card number, date and status of vaccination, age, sex, and past medical history were recorded in the computer medical system. Subsequent hospitalizations, diagnosis, ICU or coronary care unit (CCU) admissions, and deaths were captured and retrieved from the computer medical system.

Participants were allowed to choose their vaccination strat-
Figure 1. A, Comparison of the 23-valent pneumococcal polysaccharide vaccine (PPV)–trivalent influenza vaccine (TIV) group versus the unvaccinated group for hospitalization, intensive care unit (ICU) and coronary care unit (CCU) admissions, and death. B, Comparison of the TIV-alone group and the unvaccinated group for hospitalization, ICU and CCU admissions, and death. C, Comparison of the PPV-alone group and the unvaccinated group for hospitalization, ICU and CCU admissions, and death. Adjusted factors were sex and chronic obstructive pulmonary disease (COPD) comorbidity. CI, confidence interval; HR, hazard ratio.

egies (PPV plus TIV, PPV alone, TIV alone, or no vaccination). Participants who declined dual vaccination were recruited as control subjects in 1 of 3 control groups: recipients of PPV alone, recipients of TIV alone, and persons who received no vaccination. Participants who received PPV were given intramuscular Pneumovax (Pasteur Merieux). All participants except the PPV-alone group and the unvaccinated group were invited to receive intramuscular 2007–2008 and 2008–2009 TIV. All TIV belonged to the trivalent, split-virion, influenza vaccine (Vaxigrip; Sanofi Pasteur), which contained 15 μg of hemagglutinin of the following 3 strains: A/Solomon Islands/3/2006(H1N1), A/Wisconsin/67/2005(H3N2), and B/Malaysia/2506/2004 for the 2007–2008 season and A/Brisbane/59/2007(H1N1), A/Brisbane/10/2007(H3N2), and B/Florida/4/2006 for 2008–2009 season.

Primary and Secondary End Points
All enrolled participants were monitored via the computer medical system from the time of vaccination until 31 March 2009 (week 64 from the commencement of study). All diagnosis and comorbidities were standardized on the basis of The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), which was incorporated into the computer medical system with the conditions’ respective diagnostic codes. Participants with chronic illness were defined
Figure 2. Overall cumulative survival of the 4 groups of patients after vaccination. The figure compares the 23-valent pneumococcal polysaccharide vaccine (PPV)–trivalent influenza vaccine (TIV) group with the unvaccinated, TIV-alone, and PPV-alone control groups (P<.001, by the log-rank test).

Figure 3. Cumulative incidence of hospitalization for pneumonia. The figure compares the 23-valent pneumococcal polysaccharide vaccine (PPV)–trivalent influenza vaccine (TIV) group with the unvaccinated, TIV-alone, and PPV-alone control groups (P<.001, by the log-rank test).

by the following comorbidities: asthma (493), COPD (492 and 496), ischemic heart disease (411 and 413–4), old myocardial infarction (412), cardiac failure (428), hypertension (401), diabetes mellitus (250), ischemic stroke (433–4, 436), liver disease (571), renal disease (580–589), and cancer (140–209). To minimize the potential misclassification of illness by ICD-9-CM codes, the diagnosis and comorbidities were cross-checked with the discharge summaries from the computer medical system against the ICD-9-CM codes.

Primary outcome. At week 64, we compared the rate of death due to the following diagnoses: pneumonia (480–486), COPD, asthma, influenza-like illness (487), ischemic stroke, acute myocardial infarction (AMI; 410), and cardiac failure.

Secondary outcomes. At week 64, we compared hospital, ICU, and CCU admissions associated with the diagnoses defined in the “Primary outcome” subsection and also with the diagnoses ischemic heart disease and pneumococcal pneumonia (481; confirmed by positive culture from respiratory specimens). We also compared the frequency of hospitalizations for the outcome diagnosis among the 4 groups over a 9-month period from the time of enrollment.

Confounding factors. To minimize the element of selection bias, the study was performed in the HKWC outpatient clinics, where most patients belonged to the lower socioeconomic strata and had similar levels of education. Patient compliance with medical treatment for their respective underlying disease was checked and reinforced by the clinic nurses at each visit. Un-
derlying covariates that were significantly different among the 4 groups were adjusted in the multivariate analysis. The covariates analyzed included age, sex, smoking history, and the presence of any of the comorbidities mentioned above. Physicians who made diagnoses during subsequent hospitalization of the participants were not among the investigators and were unaware of the patients’ immunization status.

Statistical Analysis
Data analysis was performed using SPSS software, version 16.0 (SPSS). The incidence of each event was calculated in person-years. The baseline characteristics of the 4 vaccination groups were compared using the χ² and Mann-Whitney U tests for categorical and continuous variables, respectively. The incidence of hospitalizations among the 4 groups was compared using the χ² test. The effectiveness of the vaccine in the prevention of first hospitalization and ICU and CCU admissions for the outcome diagnoses were estimated using multivariable Cox proportional hazard models, which we adjusted for statistically significant covariables. The log-rank test was used to assess the vaccines’ effectiveness in the prevention of mortality secondary to the outcome diagnoses. P values <.05 were considered to be statistically significant.

RESULTS
Between December 2007 and June 2008, a total of 36,636 outpatient subjects were recruited. Of these, 7292 (19.9%) received both PPV and TIV, 2076 (5.7%) received TIV alone, 1875
(5.1%) received PPV alone, and 25,393 (69.3%) were unvaccinated (Table 1). Fifty-five percent of the unvaccinated declined vaccination by choice, whereas the remaining 45% were excluded for other reasons stated in the exclusion criteria. All participants in the control groups verbally consented to be included in the study for data analysis. The majority (92.2%) of the recruited persons were community dwelling and had never received either the PPV or the 7-valent pneumococcal conjugate vaccine before. The total duration of follow-up was 45,834 person-years. Before receiving the second TIV dose, 331 participants in the PPV-TIV group and in the TIV-alone group died, and 23 participants did not return for the second TIV dose. The median age of all subjects was 75 years (range, 70–80 years), and 16,611 subjects (45.3%) were male. The baseline characteristics and risk factors associated with poor outcome were similar among the participants in each group (Table 1), except for sex and the comorbid condition of COPD.

Death
At week 64, compared with the unvaccinated group, persons in the PPV-TIV group had a 35% reduction in the risk of death secondary to the outcome diagnosis (hazard ratio [HR], 0.65; 95% CI, 0.55–0.77; P < .001), whereas those who received TIV alone had a 22% reduction (HR, 0.78; 95% CI, 0.61–1.00; P = .047) in the risk of death (Figures 1 and 2).

Hospitalization and CCU and ICU Admission

**PPV-TIV group versus the unvaccinated group.** At week 64, dual-vaccinees had a 43% reduction in pneumonia (HR, 0.57; 95% CI, 0.51–0.64; P < .001) (Figure 3), a 58% reduction in pneumococcal pneumonia (HR, 0.42; 95% CI, 0.22–0.81; P = .01), a 24% reduction in COPD (HR, 0.76; 95% CI, 0.62–0.95; P = .01), a 54% reduction in asthma (HR, 0.46; 95% CI, 0.25–0.84; P = .01), and a 32% reduction in influenza-like illness (HR, 0.68; 95% CI, 0.51–0.92; P = .01), compared with the unvaccinated group (Figure 1A). For cardiovascular and cerebrovascular diagnoses, dual-vaccinees had a 33% reduction in ischemic stroke (HR, 0.67; 95% CI, 0.54–0.83; P < .001) (Figures 1A and 4), a 35% reduction in ischemic heart disease (HR, 0.65; 95% CI, 0.54–0.78; P < .001), a 48% reduction in AMI (HR, 0.52; 95% CI, 0.38–0.71; P < .001) (Figure 5), and a 19% reduction in heart failure (HR, 0.81; 95% CI, 0.70–0.94; P = .006) (Figure 6), compared with the unvaccinated group. This resulted in a 41% reduction in the rate of CCU admission (HR, 0.59; 95% CI, 0.44–0.79; P < .001) (Figures 1A and 7) and a 55% reduction in the rate of ICU admission (HR, 0.45; 95% CI, 0.22–0.94; P = .03) (Figures 1A and 8) among the dual-vaccinees.

**PPV-TIV group versus TIV-alone group.** Compared with subjects who received TIV alone, dual-vaccinees had a 24% reduction in pneumonia (P = .008) (Figures 3 and 9A) and a 38% reduction in AMI (P = .06) (Figures 5 and 9A).

**PPV-TIV group versus PPV-alone group.** Compared with subjects who received PPV alone, dual-vaccinees had a 26% reduction in pneumonia (P = .007) (Figures 3 and 9B), a 35% reduction in AMI (P = .01) (Figures 5 and 9B), a 33% reduc-
Figure 6. Cumulative incidence of hospitalization for heart failure. The figure compares the 23-valent pneumococcal polysaccharide vaccine (PPV)–trivalent influenza vaccine (TIV) group with the unvaccinated, TIV-alone, and PPV-alone control groups ($P < .001$, by the log-rank test).

Figure 7. Cumulative incidence of admission to coronary care unit. The figure compares the 23-valent pneumococcal polysaccharide vaccine (PPV)–trivalent influenza vaccine (TIV) group with the unvaccinated, TIV-alone, and PPV-alone control groups ($P < .001$, by the log-rank test).

**Discussion**

We performed a large, prospective cohort study to assess the efficacy of dual PPV and TIV vaccination among a community-based elderly Chinese population. Previous studies of dual PPV and TIV vaccination have focused on the impact on reduction of mortality secondary to pneumonia, COPD, and invasive pneumococcal disease [4, 6–13]. Many of the previous studies of TIV or PPV alone did not explicitly state whether the patients might have taken the other vaccine at the same time, potentially confounding the results [4, 6–10]. Therefore, to our knowledge, this is the first study to have comprehensively investigated the impact of dual vaccination on hospitalization for respiratory, cardiovascular, and cerebrovascular diseases, comparing dual vaccination to receipt of TIV or PPV alone and no vaccination. The results confirmed that dual vaccination in the elderly population significantly reduced the risk of death (−35%) and CCU (−41%) and ICU (−55%) admissions, whereas receipt of TIV alone also reduced the risk of death (−22%), compared with the no vaccination.

This study demonstrated several important novel findings in the role of dual vaccination in the prevention of cardiovascular and cerebrovascular diseases. Dual vaccination reduced the risk
Figure 8. Cumulative incidence of hospitalization for admission to intensive care unit. The figure compares the 23-valent pneumococcal polysaccharide vaccine (PPV)–trivalent influenza vaccine (TIV) group with the unvaccinated, TIV-alone, and PPV-alone control groups (P<.001, by the log-rank test).

of hospitalizations for ischemic stroke (−33%), ischemic heart disease (−35%), AMI (−48%), and heart failure (−19%), compared with the rates among unvaccinated persons. A previous study by Nichol et al [16] demonstrated that administration of TIV alone reduced the risk of hospitalization for cardiovascular and cerebrovascular diseases (−16% and −19%, respectively). However, the magnitude of reduction was modest when compared with the reduction observed in the dual vaccination group in the current study, leading to a further reduction for pneumonia (−24%), AMI (−38%), ischemic stroke (−19%), and CCU (−31%) and ICU (−52%) admission. The initial question raised by Nichol et al [19], suggesting that a significant proportion of the benefits in protection against respiratory, cardiovascular, and cerebrovascular diseases could be attributable to the PPV, has been addressed by the current study.

The protective effect of dual vaccination is likely to be related to the prevention of acute infection, which can elicit both a systemic and local coronary inflammatory response. A large, retrospective case series [14] demonstrated that systemic respiratory tract infection is associated with a transient increase in the risk of cardiovascular and cerebrovascular events during the first 3 days of infection. A more recent review on the role of acute infection in triggering acute coronary syndrome suggested that the association is complex and multifactorial. This is likely to be a consequence of increased inflammatory activity, prothrombotic conditions, and biomechanical stress on the coronary arteries, disrupting and triggering thrombosis in a pre-existing advanced coronary lesion [15]. Both influenza and Streptococcus pneumoniae are the likely cause of this acute infection, especially in elderly persons. A study on 34,000 autopsies showed that, during an influenza epidemic, there was an associated 30% increase in autopsy-confirmed coronary deaths [16], whereas patients with pneumonia due to S. pneumoniae or Haemophilus influenzae had an increased risk of a concurrent acute cardiac event [17, 18]. The exact mechanism for the increased risk of coronary events is not known, although it was suggested in an animal study that immunoglobulin M antibodies generated from the PPV could impede the uptake of oxidized low-density lipoprotein by macrophages due to the molecular mimicry between S. pneumoniae and oxidized low-density lipoprotein, thereby interrupting atherosclerosis [19]. Prospective, randomized clinical trials suggested that influenza vaccine can reduce the risk of coronary [20–22] and ischemic cerebrovascular events by 50% [23], whereas a large case-control study demonstrated [24] that PPV was associated with a >50% decrease in the rate of myocardial infarction 2 years after vaccination. In the current prospective study, we have clearly shown that the effect of PPV and TIV is additive, exerting both a strong short-term and long-term effect on the prevention of cardiovascular and cerebrovascular diseases.

Apart from cardiovascular protection, our study reinforced the findings of previous studies [11–13] on the effect of dual vaccination against lower respiratory tract infection in elderly persons. Local data from the Hong Kong Centre for Health Protection (CHP) suggested that the pathogenicity of the influenza A virus circulating during the study period showed no differences when compared with other years [25]. Frequency of hospitalization for pneumonia after dual vaccination was reduced from 128 to 73 hospitalizations per 1000 person-years, compared with the rate among unvaccinated persons. It also reduced the risk of hospitalizations for pneumococcal (58%) and overall (43%) pneumonia. This risk reduction is additive between the PPV and TIV. Nevertheless, effects of dual vaccination in reduction of hospitalizations for COPD, asthma, and influenza-like illness are likely to be attributed to TIV alone, as explained by a recent study [26] suggesting that respiratory viral infection play a major role in the acute exacerbation of COPD and the effect of bacterial co-infection is minimal. The successful prevention of respiratory and cardiovascular diseases with dual vaccination resulted in a significant reduction in the risk of hospitalizations and death. All of these can be translated to direct medical care cost savings for elderly persons [27, 28]. Despite the rapidly growing elderly population, vaccination rates for PPV and TIV worldwide remained suboptimal [1, 29–31]. Public opinion has been cautious with the vaccination policy recommended by the health authority in Hong Kong [32, 33]. With this new evidence of protection.
against cardiovascular and cerebrovascular diseases, vaccination with PPV and TIV among target populations needs to be encouraged and improved [33–37] and should be implemented for free [38]. A multifaceted strategy has to be applied to increase immunization rate. Community awareness and education about the potential benefits of dual vaccination with limited risk can be promoted via different mass media [39] and health talk by infectious diseases experts, to improve vaccine use by primary care providers, health care staffs, and patients prior to hospital discharge.

There were several limitations of this study. First, the participants were not randomized because of ethical reasons. Sec-

Table 2. Comparison of the Frequency of Hospitalization for the 23-Valent Pneumococcal Polysaccharide Vaccine (PPV)–Trivalent Influenza Vaccine (TIV) Group versus That for the Unvaccinated, TIV-Alone, and PPV-Alone Groups

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Cumulative incidence of hospitalization per 1000 person-years</th>
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<tbody>
<tr>
<td></td>
<td>PPV-TIV group</td>
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<tr>
<td></td>
<td>(n = 7292)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>73</td>
</tr>
<tr>
<td>COPD</td>
<td>30</td>
</tr>
<tr>
<td>Asthma</td>
<td>10</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>22</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>32</td>
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<tr>
<td>Ischemic heart disease</td>
<td>10</td>
</tr>
<tr>
<td>AMI</td>
<td>50</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Overall hospitalization for the diagnoses above</td>
</tr>
</tbody>
</table>

**NOTE.** AMI, acute myocardial infarction; COPD, chronic obstructive pulmonary disease.

a For the PPV-TIV group versus the unvaccinated group.

b For the PPV-TIV group versus the TIV-alone group.

c For the PPV-TIV group versus the PPV-alone group.
ond, there was a relatively short follow-up period because of the unexpected emergence of the novel pandemic (H1N1) virus. Thus, the full beneficial effect of the dual vaccination remained to be expressed. Another limitation is that health-conscious persons may be the one who accept the vaccines, whereas non–health-conscious ones refuse. Differences in outcome could, therefore, be due to other factors that flow from lifestyle. Potential confounding factors including the participants’ diet and exercise habits were not available for analysis and immunocompromised patients were not assessed. There was also a potential misclassification of illness using ICD-9-CM codes for diagnosis, although this was minimized by cross-checking the diagnosis against the discharge summary. Despite these limitations, the conclusions drawn from this large prospective cohort study are highly valid as the comparison was made among participants from 4 groups of different vaccination status in a population of similar baseline characteristics, risk factors, socioeconomic strata [40], educational level, and all participants had not received PPV before. Because this study included only elderly persons with chronic illness, the results may not be generalized to the whole elderly population until completion of further study of healthy elderly subjects.

In conclusions, this study has provided strong evidence that dual vaccination with PPV and TIV protect elderly persons with chronic illness against hospitalization for respiratory, cardiovascular, and cerebrovascular diseases, thereby reducing the risk of CCU and ICU admission and of death. This risk reduction is superior to TIV or PPV alone. Dual vaccination with the PPV and TIV with the pandemic (H1N1) virus strain incorporated is an important considerations for both elderly persons and younger at-risk persons. After findings from this study were vetted by the CHP of Hong Kong, the government announced free pneumococcal vaccination for elderly persons with chronic illness in addition to the free influenza vaccination.

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Reference


