On August 13, 2014, the Advisory Committee on Immunization Practices (ACIP) recommended routine use of 13-valent pneumococcal conjugate vaccine (PCV13 [Prevnar 13, Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.]) among adults aged ≥65 years. PCV13 should be administered in series with the 23-valent pneumococcal polysaccharide vaccine (PPSV23 [Pneumovax23, Merck & Co., Inc.]), the vaccine currently recommended for adults aged ≥65 years. PCV13 was approved by the Food and Drug Administration (FDA) in late 2011 for use among adults aged ≥50 years. In June 2014, the results of a randomized placebo-controlled trial evaluating efficacy of PCV13 for preventing community-acquired pneumonia among approximately 85,000 adults aged ≥65 years with no prior pneumococcal vaccination history (CAPiTA trial) became available and were presented to ACIP (1). The evidence supporting PCV13 vaccination of adults was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework and determined to be type 2 (moderate level of evidence); the recommendation was categorized as a Category A recommendation (2). This report outlines the new recommendations for PCV13 use, provides guidance for use of PCV13 and PPSV23 among adults aged ≥65 years, and summarizes the evidence considered by ACIP to make this recommendation.

Epidemiology of Pneumococcal Disease Among Adults Aged ≥65 Years

Streptococcus pneumoniae (pneumococcus) remains a leading infectious cause of serious illness, including bacteremia, meningitis, and pneumonia, among older adults in the United States. Use of a 7-valent pneumococcal conjugate vaccine (PCV7) since 2000 and PCV13 since 2010 among children in the United States has reduced pneumococcal infections directly and indirectly among children, and indirectly among adults. By 2013, the incidence of invasive pneumococcal disease (IPD) caused by serotypes unique to PCV13 among adults aged ≥65 years had declined by approximately 50% compared with 2010, when PCV13 replaced PCV7 in the pediatric immunization schedule (3). However, in 2013 an estimated 13,500 cases of IPD occurred among adults aged ≥65 years (3). Approximately, 20%–25% of IPD cases and 10% of community-acquired pneumonia cases in adults aged ≥65 years are caused by PCV13 serotypes and are potentially preventable with the use of PCV13 in this population (3,4).

PCV13 Vaccine in Adults

On December 30, 2011, PCV13 was approved for use among adults aged ≥50 years to prevent pneumonia and invasive disease caused by S. pneumoniae serotypes contained in the vaccine. The new use for Prevnar 13 was approved under FDA’s accelerated approval pathway, which allows for earlier approval of products that provide meaningful therapeutic benefit over existing
treatments for serious and life-threatening illnesses (5). FDA defined “meaningful therapeutic benefit over existing treatments” as protection of adults aged ≥50 years from nonbacteremic pneumococcal pneumonia or nonbacteremic pneumococcal pneumonia combined with protection from IPD (7). On June 20, 2012, ACIP recommended routine use of PCV13 for adults aged ≥19 years with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid leak, or cochlear implants (6). The ACIP decision to recommend PCV13 use among adults aged ≥65 years was deferred until data became available on 1) the impact of PCV13 use in children on disease in adults (i.e., indirect effects) and 2) the efficacy of PCV13 against noninvasive pneumococcal pneumonia among adults. In accordance with accelerated approval requirements, a randomized placebo-controlled trial (CAPiTA trial) was conducted in the Netherlands among approximately 85,000 adults aged ≥65 years during 2008–2013 to verify and describe further the clinical benefit of PCV13 in the prevention of pneumococcal pneumonia (I). The results of the CAPiTA trial demonstrated 45.6% (95% confidence interval [CI] = 21.8%–62.5%) efficacy of PCV13 against vaccine-type pneumococcal pneumonia, 45.0% (CI = 14.2%–65.3%) efficacy against vaccine-type nonbacteremic pneumococcal pneumonia, and 75.0% (CI = 41.4%–90.8%) efficacy against vaccine-type IPD among adults aged ≥65 years (I).

Two randomized, multicenter, immunogenicity studies conducted in the United States and Europe among older adults showed that PCV13 induced an immune response as good as or better than that induced by PPSV23 (7,8). Functional antibody responses were measured 1 month after vaccination using an opsonophagocytic activity (OPA) assay. In adults aged 60–64 years with no prior pneumococcal vaccination, PCV13 elicited OPA geometric mean antibody titers (GMTs) to the 12 serotypes common to both vaccines that were comparable with, or higher than, responses elicited by PPSV23 (7). In adults aged ≥70 years who previously had been immunized with a single dose of PPSV23 ≥5 years before enrollment, PCV13 elicited OPA responses that were comparable with those elicited by PPSV23 for two serotypes and higher for 10 serotypes (8).

Immunogenicity studies evaluating responses to PCV7 and PPSV23 administered in series showed a better immune response when PCV7 was administered first (9–12). An evaluation of immune response after a second pneumococcal vaccination administered 1 year after the initial study doses showed that subjects who received PPSV23 as the initial study dose had lower OPA antibody responses after subsequent administration of PCV13 than those who had received PCV13 as the initial dose followed by a dose of PPSV23, regardless of the level of the initial OPA response to PPSV23 (9). Studies evaluating the immune response after a sequence of PCV7 or PCV13 followed by PPSV23 with intervals of 2, 6, and 12 months or 3–4 years demonstrated that after the PPSV23 dose, antibody levels were higher than the pre-PCV baseline, and a noninferior response was observed when compared with post-PCV antibody levels (9–12). None of the studies were designed to evaluate the optimal interval between vaccine doses.

Safety of PCV13 was evaluated in approximately 6,000 PPSV23-naïve and PPSV23-experienced adults aged ≥50 years (13). Overall incidence of serious adverse events reported within 1 month of an initial study dose of PCV13 or PPSV23 did not differ between the two vaccines and ranged from 0.2% to 1.7%. From 1 to 6 months after an initial study dose, the overall incidence of serious adverse events ranged from 1.2% to 5.8% among persons vaccinated with PCV13 and 2.4% to 5.5% among persons vaccinated with PPSV23. Rates of reported serious adverse events in the treatment groups were similar among studies that enrolled PPSV23-naïve subjects and studies that enrolled PPSV23-experienced subjects. Common adverse reactions reported with PCV13 were pain, redness, and swelling at the injection site; limitation of movement of the arm in which the injection was given; fatigue; headache; chills; decreased appetite; generalized muscle pain; and joint pain. Similar reactions were observed in adults who received PPSV23 (13).
Indirect effects from PCV13 use among children, if similar to those observed after PCV7 introduction, might further reduce the remaining burden of adult pneumococcal disease caused by PCV13-types. A preliminary analysis using a probabilistic model following a single cohort of persons aged 65 years demonstrated that adding a dose of PCV13 to the current PPSV23 recommendations for adults aged ≥65 years, compared with current PPSV23 recommendations, would lead to additional health benefits (14). This strategy would prevent an estimated 230 cases of IPD and approximately 12,000 cases of community-acquired pneumonia over the lifetime of a single cohort of persons aged 65 years, assuming current indirect effects from the child immunization program and current PPSV23 vaccination coverage among adults aged ≥65 years (approximately 60%). In a setting of fully realized indirect effects assuming the same vaccination coverage, the expected benefits of PCV13 use among this cohort will likely decline to an estimated 160 cases of IPD and 4,500 cases of community-acquired pneumonia averted among persons aged ≥65 years (14).

CDC will assess the implementation and impact of the recommendation for PCV13 use among adults aged ≥65 years, including coverage with PCV13 and PPSV23, and impact of PCV13 on vaccine-type IPD burden and community-acquired pneumonia. Monitoring disease trends among adults who do not receive PCV13 might help quantify indirect effects and the long-term utility of routine PCV13 use among adults. ACIP will be updated routinely on changes in the burden of IPD and community-acquired pneumonia among adults during the next 3 years to determine the need for revisions to the adult PCV13 recommendations.

PPSV23 in Adults

A single dose of PPSV23 is recommended for routine use in the United States among adults aged ≥65 years (15). Effectiveness of PPSV23 in preventing IPD in adults has been demonstrated, but the data on the effectiveness of this vaccine in preventing noninvasive pneumococcal pneumonia among adults aged ≥65 years have been inconsistent. PPSV23 contains 12 serotypes in common with PCV13 and 11 additional serotypes. In 2013, 38% of IPD among adults aged ≥65 years was caused by serotypes unique to PPSV23 (3). Given the high proportion of IPD caused by serotypes unique to PPSV23, broader protection is expected to be provided through use of both PCV13 and PPSV23 in series. ACIP considered multiple factors when determining the optimal interval between a dose of PCV13 and PPSV23, including immune response, safety, the risk window for protection against disease caused by serotypes unique to PPSV23, as well as timing for the next visit to the vaccination provider.

ACIP Recommendations for PCV13 and PPSV23 Use

Both PCV13 and PPSV23 should be administered routinely in series to all adults aged ≥65 years (Box).

Pneumococcal vaccine-naïve persons. Adults aged ≥65 years who have not previously received pneumococcal vaccine or whose previous vaccination history is unknown should receive a dose of PCV13 first, followed by a dose of PPSV23. The dose of PPSV23 should be given 6–12 months after a dose of PCV13. If PPSV23 cannot be given during this time window, the dose of PPSV23 should be given during the next visit. The two vaccines should not be coadministered, and the minimum acceptable interval between PCV13 and PPSV23 is 8 weeks.

Previous vaccination with PPSV23. Adults aged ≥65 years who have previously received ≥1 doses of PPSV23 also should receive a dose of PCV13 if they have not yet received it. A dose of PCV13 should be given ≥1 year after receipt of the most recent PPSV23 dose. For those for whom an additional dose of PPSV23 is indicated, this subsequent PPSV23 dose should be given 6–12 months after PCV13 and ≥5 years after the most recent dose of PPSV23 (15).

Potential Time-Limited Utility of Routine PCV13 Use Among Adults ≥65 Years. The recommendations for routine PCV13 use among adults aged ≥65 years will be reevaluated in 2018 and revised as needed.

ACIP recommendations for routine use of PCV13 in adults aged ≥19 years with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid leak, or cochlear implants remain unchanged (6).

Coadministration with Other Vaccines

Concomitant administration of PCV13 and trivalent inactivated influenza vaccine (TIV) has been demonstrated to be immunogenic and safe. PCV13 can be coadministered with TIV in an adult immunization program. However, a randomized double-blind trial found slightly lower pneumococcal serotype–specific geometric mean concentrations and lower proportion achieving at least a fourfold rise in hemagglutination inhibition assay titer for one of three influenza subtypes (influenza A[H3N2]) with PCV13 plus TIV compared with PCV13 alone or TIV alone among adults aged ≥65 years (16). Currently, no data are available on coadministration with other vaccines (e.g., tetanus, diphtheria, and acellular pertussis vaccine or zoster vaccine) among adults.

Precautions and Contraindications

Before administering PCV13, vaccination providers should consult the package insert for precautions, warnings, and contraindications. Vaccination with PCV13 is contraindicated in persons known to have a severe allergic reaction (e.g., anaphylaxis) to any component of PCV13 or PCV7 or to any diphtheria toxoid–containing vaccine.

Adverse events occurring after administration of any vaccine should be reported to the Vaccine Adverse Event Reporting System (VAERS). Reports can be submitted to VAERS online, by fax,
Sequential administration and recommended intervals for PCV13 and PPSV23 for adults aged ≥65 years — Advisory Committee on Immunization Practices, United States

Pneumococcal vaccine-naïve persons aged ≥65 years

- PCV13 at age ≥65 years
- PPSV23

Persons who previously received PPSV23 at age ≥65 years

- PPSV23 already received at age ≥65 years
- PCV13

Persons who previously received PPSV23 before age 65 years who are now aged ≥65 years

- PPSV23 already received at age <65 years
- PCV13 at age ≥65 years
- PPSV23

Abbreviations: PCV13 = 13-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine.

* Minimum interval between sequential administration of PCV13 and PPSV23 is 8 weeks; PPSV23 can be given later than 6–12 months after PCV13 if this window is missed.

or by mail. Additional information about VAERS is available by telephone (1-800-822-7967) or online (http://vaers.hhs.gov).

Acknowledgments


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References


Announcement

Now Available Online: Final 2013–14 Influenza Vaccination Coverage Estimates for Selected Local Areas, States, and the United States

Final 2013–14 influenza season vaccination coverage estimates are now available online at FluVaxView (http://www.cdc.gov/flu/fluvoxview). The online information includes estimates of the cumulative percentage of persons vaccinated by the end of each month, from July 2013 through May 2014, for select local areas, each state, each U.S. Department of Health and Human Services region, and the United States overall.

Analyses were conducted using National Immunization Survey influenza vaccination data for children aged 6 months–17 years and Behavioral Risk Factor Surveillance System data for adults aged ≥18 years. Estimates are provided by age group and race/ethnicity. These estimates are presented in an interactive report (http://www.cdc.gov/flu/fluvoxview/interactive.htm) and complemented by an online summary report (http://www.cdc.gov/flu/fluvoxview/coverage-1314estimates.htm).
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
Table 1. Baseline Characteristics of the 36,636 Study Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unvaccinated persons (n = 25,393)</th>
<th>PPV-TIV group (n = 7292)</th>
<th>TIV-alone group (n = 2076)</th>
<th>PPV-alone group (n = 1875)</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td>Age, median years (range)</td>
<td>75 (70–80)</td>
<td>77 (71–83)</td>
<td>75 (70–80)</td>
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<td>40</td>
<td>45</td>
<td>45</td>
<td>&lt;.001</td>
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<tr>
<td>Asthma</td>
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<td>2.2</td>
<td>2.2</td>
<td>2.8</td>
<td>.42</td>
</tr>
<tr>
<td>COPD</td>
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<td>4.4</td>
<td>4.6</td>
<td>3.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
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<td>7.6</td>
<td>7.2</td>
<td>7.3</td>
<td>.64</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.2</td>
<td>1.4</td>
<td>1.3</td>
<td>1.0</td>
<td>.33</td>
</tr>
<tr>
<td>Heart failure</td>
<td>7.9</td>
<td>7.6</td>
<td>7.9</td>
<td>8.7</td>
<td>.40</td>
</tr>
<tr>
<td>Hypertension</td>
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<td>60.5</td>
<td>60.6</td>
<td>59.8</td>
<td>.91</td>
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<tr>
<td>Diabetes mellitus</td>
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<td>24.6</td>
<td>24.5</td>
<td>.10</td>
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<tr>
<td>Ischemic stroke</td>
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<td>7.8</td>
<td>7.5</td>
<td>7.4</td>
<td>.33</td>
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<tr>
<td>Chronic liver disease</td>
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<td>0.2</td>
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<td>.55</td>
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<tr>
<td>Chronic renal disease</td>
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<td>2.5</td>
<td>2.6</td>
<td>.85</td>
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<tr>
<td>Cancer</td>
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<td>13.8</td>
<td>14.8</td>
<td>.21</td>
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</table>

NOTE. Data are percentage of subjects, unless otherwise indicated. COPD, chronic obstructive pulmonary disease; PPV, 23-valent pneumococcal polysaccharide vaccine; TIV, trivalent influenza vaccine.

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.
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. Underlying 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).

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 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).
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 coinfection 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>PPV-TIV group</th>
<th>Unvaccinated group</th>
<th>TIV-alone group</th>
<th>PPV-alone group</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( (n = 7292) )</td>
<td>( (n = 25,393) )</td>
<td>( (n = 2076) )</td>
<td>( (n = 1875) )</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>73</td>
<td>128</td>
<td>.001</td>
<td>.003</td>
<td>.31</td>
</tr>
<tr>
<td>COPD</td>
<td>30</td>
<td>38</td>
<td>.05</td>
<td>.48</td>
<td>.11</td>
</tr>
<tr>
<td>Asthma</td>
<td>3</td>
<td>8</td>
<td>.03</td>
<td>4</td>
<td>.24</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>10</td>
<td>16</td>
<td>.002</td>
<td>.005</td>
<td>.14</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>22</td>
<td>36</td>
<td>.001</td>
<td>.007</td>
<td>.004</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>32</td>
<td>56</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.56</td>
</tr>
<tr>
<td>AMI</td>
<td>10</td>
<td>21</td>
<td>.001</td>
<td>19</td>
<td>.007</td>
</tr>
<tr>
<td>Heart failure</td>
<td>50</td>
<td>76</td>
<td>.001</td>
<td>63</td>
<td>.40</td>
</tr>
<tr>
<td>Overall hospitalization for the diagnoses above</td>
<td>222</td>
<td>308</td>
<td>&lt;.001</td>
<td>252</td>
<td>.16</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 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


