Acute Respiratory Illness in Patients With COPD and the Effectiveness of Influenza Vaccination*

A Randomized Controlled Study

Phunsup Wongsurakiat, MD, FCCP; Khun Nanta Maranetra, MD; Chantapong Wasi, MD; Uraiwan Kositanont, MD; Wanchai Dejsomritrutai, MD, MSc; and Suchai Charoenratanakul, MD, FCCP

**Study objectives:** To determine the effectiveness of influenza vaccination on influenza-related acute respiratory illness (ARI) and overall ARI in patients with COPD, and its relationship to the degree of airflow obstruction.

**Design:** Stratified, randomized, double-blind, placebo-controlled trial.

**Setting:** From June 1997 to November 1998 at a single university hospital.

**Patients and interventions:** One hundred twenty-five patients with COPD were stratified based on their FEV₁ as having mild, moderate, and severe COPD. Within each group, they were randomized to the vaccine group (62 patients who received purified, trivalent, split-virus vaccine) or the placebo group (63 patients).

**Measurements:** The number of episodes and severity of total ARI, classified as outpatient treatment, hospitalization, and requirement of mechanical ventilation; and the number of episodes and severity of influenza-related ARI.

**Results:** The incidence of influenza-related ARI was 28.1 per 100 person-years and 6.8 per 100 person-years in the placebo group and vaccine group, respectively (relative risk [RR], 0.24 [p = 0.005]; vaccine effectiveness, 76%). The incidences were 28.2, 23.8, and 31.2 per 100 person-years in the patients with mild, moderate, and severe COPD, respectively, in the placebo group, and 4.5, 13.2, and 4.6 per 100 person-years in the patients with mild, moderate, and severe COPD, respectively, in the vaccine group (RR, 0.16 [p = 0.06]; vaccine effectiveness, 84%; RR, 0.55 [p = 0.5]; vaccine effectiveness, 45%; and RR, 0.15 [p = 0.04]; vaccine effectiveness, 85%, in the patients with mild, moderate, and severe COPD, respectively). Bivariate analysis revealed that the effectiveness of influenza vaccination was not modified by the severity of COPD, comorbid diseases, age, gender, or current smoking status. There was no difference in the incidence or severity of total ARI between the placebo group and the vaccine group.

**Conclusions:** Influenza vaccination is highly effective in the prevention of influenza-related ARI regardless of the severity of COPD. Influenza vaccination does not prevent other ARI unrelated to influenza. The effectiveness of influenza vaccination in the prevention of overall ARI in patients with COPD will depend on how much the proportion of influenza-related ARI contributes to the incidence of total ARI. Influenza vaccination should be recommended to all patients with COPD.

**Key words:** acute exacerbation; common cold; hospitalization; mechanical ventilation; viral infection

**Abbreviations:** ARI = acute respiratory illness; GMT = geometric mean titer; HI = hemagglutination inhibition; RR = relative risk

COPD is a common disease, and evidence shows that the prevalence of COPD is increasing worldwide. COPD imposes a large financial burden on the health service. It now ranks fifth in terms of global burden of disease.¹ Most of the morbidity, mortality, and health-care costs of patients with COPD are related to the exacerbation of COPD.² ³ Viral infection plays an important role in the exacerbation of COPD.⁴ ⁵ It may be the cause of one third of these exacerbations. A significant causative virus related to these exacerbation is influenza virus.⁶ In addition, viral infections may impair host defenses,⁷ ⁸ which leads to increased colonization or infection with pathogenic bacteria. Thus, prevention of influenza virus infection in patients with COPD may substantially...
regarding the efficacy and cost-effectiveness of influenza vaccination in reducing the number of hospitalizations, pneumonia, and deaths among elderly people and individuals with high-risk chronic conditions. Most of this evidence comes from observational studies. There is little direct information in the form of randomized controlled studies regarding the effectiveness of influenza immunization in patients with COPD. Moreover, the study periods of those studies were short, much less than 1 year, and the results are contradictory. One study reported significantly fewer episodes of both influenza-related exacerbation and overall exacerbation in the vaccinated group during a study period of 4 months. Another study reported more respiratory symptoms in the vaccinated group than the placebo group during a study period of 18 weeks. Also, patients with COPD are a heterogeneous group regarding the effectiveness of influenza immunization. These patients are also elderly with chronic illness that may lead to lower immune response to immunization with a shorter duration of protection. Thus, we conducted a randomized, double-blind, placebo-controlled trial to determine the effectiveness of influenza vaccination in the prevention of ARI related to influenza virus infection and overall ARI in patients with COPD and its relationship to the degree of airflow obstruction.

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A stratified, randomized, double-blind, placebo-controlled study was conducted from June 1997 to October 1998 at a university hospital in Bangkok, Thailand. Subjects were recruited from patients with COPD who attended our COPD clinic regularly. They were eligible for this trial if they had a clinical diagnosis of COPD together with an FEV1 of < 70% of the FVC, and a < 15% increase in FEV1 after an inhaled bronchodilator. Patients excluded were those who had a history of allergy to eggs, were immuno compromised or receiving any immuno suppressive drug except corticosteroids, or had associated malignancy or any disease that would be likely to shorten their survival to < 1 year.

Study Protocol and Testing

Demographic data, comorbid diseases, and history of cigarette smoking were collected for all patients studied. The patients were placed on a standard treatment regimen according to the Thai guidelines for the management of COPD. Baseline evaluation of clinical symptoms and lung functions were performed. When stable, without an acute respiratory illness (ARI), patients were seen at our COPD clinic at 4-week intervals. On the first visit, patients were informed about possible symptoms of ARI. Patients were told to notify the center immediately if they had these symptoms. At each monthly visit, they were also asked about episodes of respiratory illness during the past month. The study protocol was approved by the institutional ethics committee, and informed consent was obtained from all subjects.

Randomization and Vaccination

All participants were stratified based on their FEV1 as mild COPD (FEV1 ≤ 70% predicted), moderate COPD (FEV1 50 to 69% predicted), and severe COPD (FEV1 < 50% predicted). In each severity stratum, each patient was numbered consecutively. These numbers had been previously randomized to either the vaccine group or the placebo group. At the vaccination session, each patient number was identified. The patient then received an IM injection with influenza vaccine or placebo in the deltoid muscle according to the previously randomized identification number. The process of checking the identification number and vaccine or placebo injection were performed solely by a nurse who did not participate in the care of these patients. The vaccine used was the purified, trivalent, split-virus vaccine (Pasteur Merieux; Lyon, France). Each dose (0.5 mL) contained influenza A/Texas/36/91 (H1N1), A/Nanchang/933/95 (H3N2), and B/Harbin/07/94, all with 15 µg of hemagglutinin. These antigens were in accordance with the recommendation of the World Health Organization; 0.5 mL of vitamin B1 was used as placebo. Every patient received two doses of the vaccine or placebo, with the second dose administered 4 weeks after the first dose. We used a two-dose vaccination schedule because influenza vaccine had just become available in our country and our patients with COPD had never been vaccinated. For children 9 years of age who have never been vaccinated, a second dose of influenza vaccine is recommended.

Blood Tests

Ten milliliters of venous blood were obtained from each patient at the first dose of vaccine or placebo injection, at the second dose of vaccine or placebo injection, at 4 weeks, at 6 months, and at 1 year (B5) after the first dose of vaccine or placebo injection. These venous blood samples were tested for influenza antibody titer by means of the hemagglutination inhibition (HI) test.
Protocol During an ARI

Whenever the patients had an ARI, their clinical characteristics were recorded. The clinical characteristics of each ARI were classified as one of four types: common cold, influenza-like illness, acute exacerbation of COPD, and pneumonia. Common cold was defined as an infection of the upper respiratory tract with predominating rhinitis and pharyngitis. Influenza-like illness was defined when the patients had symptoms of generalized aches, fever, and headache with or without upper respiratory tract symptoms. Acute exacerbation of COPD was defined by these criteria: (1) increased dyspnea, (2) increased sputum volume, and (3) increased sputum purulence. An exacerbation was diagnosed when at least two of the three symptoms, or one of these symptoms in addition to at least one of the following were found: (1) upper respiratory tract infection (sore throat, nasal discharge) within the past 5 days, (2) fever without any other cause, (3) increased wheezing, (4) increased cough, and (5) an increase in respiratory rate or heart rate by 20% as compared with baseline. Pneumonia was diagnosed when the patients had compatible symptoms plus new infiltrates shown on their chest radiographs. For each ARI, the severity was classified as outpatient treatment, needing hospitalization, and requiring mechanical ventilation. In case of hospitalization, the duration of hospital admission as well as the outcome of treatment (improved or dead) were also recorded.

For each ARI, paired venous blood samples were obtained from the patient when first seen to test for influenza HI antibody titer (acute serum) and 4 to 6 weeks afterwards (convalescent serum). If the duration of the ARI was < 6 days, a throat swab, a nasal swab, and a sputum specimen were also collected for viral culture.

Laboratory Measurements

Antibodies to influenza viruses were detected by the HI test. The influenza virus strains of the vaccine were used for the titrations. The titer was defined as the reciprocal of the highest dilution that gave a positive reaction. From the results of the determinations per serum and per antigen, the geometric mean titer (GMT) was used for further calculations. Negative titers (< 10) were arbitrarily regarded as 5.

Nasal swabs, throat swabs, and sputum obtained were placed in 3 mL of viral transport media and used for viral isolation. Pellets of sputum were further investigated for the presence of respiratory viral antigen by indirect immunofluorescence.

Diagnostic Criteria

A fourfold HI titer increase in convalescent serum compared to acute serum with a titer of ≥ 40 and/or demonstration of influenza antigen with or without positive culture finding was considered as meeting the criteria for influenza virus infection. An episode of ARI with evidence of influenza virus infection was classified as influenza-related ARI.

Statistical Analysis

We sized the study with the assumption that the incidence of influenza-related respiratory illness in patients with COPD was approximately 30%,17 and the effectiveness of influenza vaccination was 70%. With an α of 0.05 (two-sided test) and a power of 80%, the number of patients needed would be 58 in each group. Statistical analysis was carried out using SPSS statistical software (SPSS; Chicago, IL). χ² and t tests were used to compare groups for discrete and continuous variables, respectively. The incidence of ARI in the vaccine and placebo groups was calculated and compared using an incidence density ratio (the ratio of the number of episodes of ARI over the number and time of follow-up of patients [person-years]), estimated by a Poisson model, and then calculating the relative risk (RR) and the effectiveness of influenza vaccination (1 – RR). Serology titers were expressed as the reciprocal of the highest serum dilution. Kaplan-Meier survival analysis was used to calculate the probability of not acquiring influenza-related ARI and overall ARI over the study year; a p value of 0.05 was considered the limit of significance. All p values were two sided.

RESULTS

One hundred thirty-two consecutive patients with COPD who attended our COPD clinic regularly were evaluated for enrollment in to this study. Seven patients were excluded because they could not attend the clinic at 4-week intervals. One hundred twenty-five patients with COPD were recruited to this study: 62 patients were in the vaccine group, and 63 patients were in the placebo group. There were three patients who dropped out of the study: one patient in the vaccine group, and two patients in the placebo group. Five patients in the vaccine group and three patients in the placebo group died from diseases or conditions not related to ARI. Data from these patients were retained in the analyses as possible. One patient in the vaccine group received only one dose of influenza vaccine because of a skin rash developing after the first injection. This patient’s blood samples were excluded from the analysis of immune response after influenza vaccination. There were two missing baseline blood samples; one sample in the vaccine group, and one sample in the placebo group. Therefore, the blood samples of the 60 patients were finally included in the analysis of immune response after influenza vaccination.

Characteristics of All Study Subjects

The baseline characteristics of both groups are shown in Table 1. Approximately 30% of the patients in each group had comorbid diseases, which were hypertension, coronary artery diseases, and diabetes. Half the patients had a previous infection by at least one subtype of influenza virus type A, and approximately 20% had been infected with influenza virus type B strain in the vaccine used as shown by an HI titer ≥ 10. However, their GMTs were at a low level. Half the patients with influenza type A infection and 20% of those with influenza type B infection had HI titers greater than the protective threshold (≥ 40), as shown in Table 2.

Antibody Response After Influenza Vaccination

In Table 3, the HI antibody response expressed by fourfold response rate, postvaccination reciprocal of
GMT, and protection rate (HI titer ≥ 40) are presented. There were high response rates and high protection rates after the first dose vaccination except for influenza type B. There were very low response rates after the second dose vaccination.

**Effectiveness of Influenza Vaccination on ARI Related to Influenza Virus Infection**

Seventeen unvaccinated patients and 4 vaccinated patients acquired ARI together with a fourfold rising in HI antibody (influenza-related ARI) during the study year as shown in Table 4. There was another one vaccinated patient who had a fourfold increase in his HI titer against influenza A (H3N2) without ARI symptoms. A total of 165 specimens of throat swab, nasal swab, and sputum were collected for viral culture during the ARI, 3 of which were positive for influenza virus (2 specimens were positive on viral culture and 1 specimen was positive by indirect immunofluorescence test). All these patients had a fourfold rise in serum HI antibody. Twenty of 21 episodes (95%) of influenza infection were influenza type A. Only one patient had an ARI from influenza type B.

The incidence and severity of influenza-related ARI are shown in Table 4. The incidence per patient of influenza-related ARI in the placebo group in the study year was approximately 28.1 per 100 person-years (one patient had one episode of influenza infection). The incidence per episode of ARI was lower, only 11.7% (17 of a total of 145 episodes of ARI in the placebo group). The incidence was similar, in the range of 20 to 30%, in all three subgroups of severity of airflow obstruction. Vaccination against influenza was associated with significantly fewer episodes of influenza-related ARI. The overall effectiveness of influenza vaccination revealed that the effectiveness of influenza vaccination was consistent regardless of age, gender, severity of COPD, smoking status, or comorbid diseases: crude incidence rate ratio of influenza-related ARI of vaccine group over placebo group adjusted for age (< 70

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**Table 1—Baseline Characteristics of All Study Subjects**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Vaccine Group (n = 62)</th>
<th>Placebo Group (n = 63)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>67.6 ± 8</td>
<td>69.1 ± 7</td>
<td>0.3</td>
</tr>
<tr>
<td>Male/female gender, No.</td>
<td>59/3</td>
<td>59/4</td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>3 (5)</td>
<td>2 (3)</td>
<td>0.7</td>
</tr>
<tr>
<td>Current smoker</td>
<td>12 (19)</td>
<td>12 (19)</td>
<td>1</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>47 (76)</td>
<td>49 (78)</td>
<td>0.8</td>
</tr>
<tr>
<td>Severity of COPD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 ≥ 70% predicted</td>
<td>23 (37)</td>
<td>22 (35)</td>
<td>0.8</td>
</tr>
<tr>
<td>FEV1 50–69% predicted</td>
<td>16 (26)</td>
<td>17 (27)</td>
<td>0.9</td>
</tr>
<tr>
<td>FEV1 &lt; 50% predicted</td>
<td>23 (37)</td>
<td>24 (38)</td>
<td>0.9</td>
</tr>
<tr>
<td>Having comorbid diseases</td>
<td>23 (37)</td>
<td>18 (20)</td>
<td>0.3</td>
</tr>
<tr>
<td>Systemic steroid use</td>
<td>1 (2)</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Inhaled steroid use</td>
<td>21 (34)</td>
<td>19 (30)</td>
<td>0.8</td>
</tr>
<tr>
<td>Inhaled long-acting β₂-agonist use</td>
<td>2 (3)</td>
<td>1 (2)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD or No. (%) unless otherwise indicated.
†Vaccine group vs placebo group by independent-sample t test.

**Table 2—Baseline Influenza HI Antibody Titer of All Study Subjects**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Vaccine Group (n = 61)</th>
<th>Placebo Group (n = 62)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with HI titer ≥ 10 at first blood sample against:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/Texas/36/91 (H1N1)</td>
<td>27 (44)</td>
<td>35 (56)</td>
<td>0.2</td>
</tr>
<tr>
<td>A/Nanchang/933/95 (H3N2)</td>
<td>34 (56)</td>
<td>33 (53)</td>
<td>0.8</td>
</tr>
<tr>
<td>B/Harbin/7/94</td>
<td>13 (21)</td>
<td>9 (14)</td>
<td>0.4</td>
</tr>
<tr>
<td>Reciprocal GMT titer of first blood sample against:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/Texas/36/91 (H1N1)</td>
<td>10.9</td>
<td>12.6</td>
<td>0.4</td>
</tr>
<tr>
<td>A/Nanchang/933/95 (H3N2)</td>
<td>14.2</td>
<td>16.3</td>
<td>0.1</td>
</tr>
<tr>
<td>B/Harbin/7/94</td>
<td>6.9</td>
<td>6</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%) unless otherwise indicated.
†Comparing vaccine group and placebo group by χ² test.
years or ≥ 70 years), gender (male or female), current smoking status (yes or no), comorbid diseases (yes or no), and severity of COPD (mild or moderate or severe) were 0.24, 0.24, 0.24, 0.22, and 0.24, respectively, with p values for effect modification of 0.3, 0.8, 0.6, 0.1, and 0.5, respectively; crude incident rate ratio of hospitalization from influenza-related ARI of vaccine group over placebo group = 0.41; by Mantel-Haenszel test, incident rate ratios of hospitalization from influenza-related ARI of vaccine group over placebo group adjusted for age (< 70 years or ≥ 70 years), gender (male or female), current smoking status (yes or no), comorbid diseases (yes or no), and severity of COPD (mild or moderate or severe) were 0.38, 0.42, 0.41, 0.38, and 0.4, respectively, with p values for effect modification of 0.3, 0.8, 0.8, 0.9, and 1, respectively.

**Clinical Presentations**

The clinical presentations of overall ARI and influenza-related ARI are shown in Table 5. The most common presentation of ARI in patients with COPD was acute exacerbation, which was found in 161 of 269 episodes (59.8%) of all ARIs. It was also the most common presentation of influenza-related ARI (13 of 21 episodes, 61.9%). There was no significant difference in the incidence of acute exacerbation between patients in the vaccine group and placebo group. The most specific clinical presentation for influenza-related ARI was influenza-like illness, of which the incidence rate was significantly lower in the vaccine group compared to the placebo group. Pneumonia was the least common presentation, and none of it was related to influenza.

**Timing of Influenza Activity**

There were episodes of ARI related to influenza occurring all-year round: one episode in January, one episode in February, one episode in March, five episodes in May, three episodes in June, one episode in July, two episodes in August, four episodes in September, one episode in November, and two episodes in December. The peak incidence of influenza occurred from May to September, the rainy season. Influenza vaccination provided effective protection against ARI related to influenza throughout the study year, as shown by a significant difference in the probability of not acquiring influenza-related ARI between patients in the vaccine group and the placebo group (Fig 1).

**Effectiveness of Influenza Vaccination on Total ARI**

There were 269 episodes of ARI during the study year. The incidence of ARI, demonstrated by the probability of not acquiring ARI over the study year, was not different between the vaccine group and placebo group as shown in Figure 2. Also, there was no difference in the probability of not being hospitalized related to ARI (p = 0.2 by log-rank test) and the probability of not receiving mechanical ventilation related to ARI (p = 0.4 by log-rank test) over the study year between the vaccine group and placebo group (data not shown).

**Discussion**

This study is a randomized clinical trial regarding influenza vaccination in patients with COPD, which used rigid criteria (clinical diagnosis of ARI plus serologic evidence of influenza) in the diagnosis of influenza. It demonstrated that influenza vaccination was highly effective in the prevention of ARI related to influenza virus infection.

The years 1997 and 1998 were not influenza epidemic years in Thailand. Data from the virus Research Institute, Department of Medical Sciences, Ministry of Public Health17 showed that most of the influenza viruses isolated from the patients with ARI was influenza A/Sydney/5/97 (H3N2). This virus strain was closely related to the influenza A/Nanchang/933/96 (H3N2) in the vaccine used in this study. However, because the study year was not an epidemic influenza period, the incidence of influenza was low. The incidence of influenza virus infection in patients with chronic bronchitis varies from 6 to 30%. 3, 5, 17, 24 Although the incidence of influenza...
<table>
<thead>
<tr>
<th>Variables</th>
<th>V (n = 23)</th>
<th>P (n = 22)</th>
<th>RR (95% CI)</th>
<th>p Value</th>
<th>V (n = 16)</th>
<th>P (n = 17)</th>
<th>RR (95% CI)</th>
<th>p Value</th>
<th>V (n = 23)</th>
<th>P (n = 24)</th>
<th>RR (95% CI)</th>
<th>p Value</th>
<th>V (n = 62)</th>
<th>P (n = 63)</th>
<th>RR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients and time of follow-up, person-yr</td>
<td>22 (1.4)</td>
<td>21.3 (1.3)</td>
<td>15.2 (0.05–3.8)</td>
<td>0.06</td>
<td>1 (2.4)</td>
<td>2 (3.3)</td>
<td>0.2 (0.003–1.3)</td>
<td>0.06</td>
<td>21.6 (1.3)</td>
<td>22.4 (1.4)</td>
<td>58.8 (0.003–1.1)</td>
<td>0.04</td>
<td>4 (6.8)</td>
<td>17 (28.1)</td>
<td>0.2 (0.06–0.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>All ARI episodes (IR)</td>
<td>0 (0)</td>
<td>4 (18.8)</td>
<td>0.2 (0.003–1.3)</td>
<td>0.06</td>
<td>1 (2.4)</td>
<td>2 (3.3)</td>
<td>0.2 (0.003–1.3)</td>
<td>0.06</td>
<td>0 (0–1.1)</td>
<td>0 (0–1.1)</td>
<td>0.03</td>
<td>2 (3.4)</td>
<td>12 (28.1)</td>
<td>0.2 (0.02–0.8)</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Hospitalization episode (IR)</td>
<td>1 (4.5)</td>
<td>2 (9.4)</td>
<td>0.5 (0.003–1.3)</td>
<td>0.06</td>
<td>1 (2.4)</td>
<td>2 (3.3)</td>
<td>0.2 (0.003–1.3)</td>
<td>0.06</td>
<td>2 (3.4)</td>
<td>5 (8.3)</td>
<td>0.4 (0.04–2.5)</td>
<td>0.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation episode (IR)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0–1.1)</td>
<td>0.03</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0–1.1)</td>
<td>0.03</td>
<td>0 (0)</td>
<td>3 (5)</td>
<td>0 (0–2.5)</td>
<td>0.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Each patient had only one episode of influenza-related ARI. The number of episodes of hospitalization also included episodes of mechanical ventilation. V = vaccine group; P = placebo group; IR = incidence rate (No. of episodes/100 person-years); CI = confidence interval.

†Significant difference comparing the incident rate of influenza-related ARI between vaccine group and the placebo group. Effectiveness of influenza vaccination (%) = (1 − RR) × 100; overall effectiveness of influenza vaccination = 76%; effectiveness of influenza vaccination was 84%, 45%, and 85% for mild, moderate, and severe COPD, respectively.
influenza was low, the effectiveness of influenza vaccination in patients with COPD was clearly shown in this study. Although most of our patients were elderly, the effectiveness of vaccination in the prevention of influenza-related ARI was 76%. This was higher than most of the reported effectiveness of influenza vaccination in elderly population in which the effectiveness ranged from 30 to 50%.13,14,18,28 This high effectiveness is most likely explained by the good immune response of these patients after vaccination, the close relation between the circulating viruses and the strains of viruses in vaccine used, and partly because of the rigid diagnostic criteria used in this study; therefore, the real effect of vaccination was not diluted by false-positive diagnosis influenza as in many previous reports12,13,18,28 that used only clinical diagnostic criteria. This is supported by the study of Govaert and coworkers,14 in which the effectiveness of influenza vaccination in the reduction of clinical plus serologic influenza was higher than the effectiveness on clinical influenza only. Furthermore, our patient population was more

Table 5—Clinical Presentation of ARI in Patients With COPD

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Vaccine (58.8 P-Y), No. of Patients (IR)</th>
<th>Placebo (60.5 P-Y), No. of Patients (IR)</th>
<th>RR (95% CI)</th>
<th>p Value</th>
<th>Total (119.3 P-Y), No. of Patients (IR)</th>
<th>Influenza, No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common cold</td>
<td>43 (0.7)</td>
<td>42 (0.7)</td>
<td>1.05 (0.67–1.6)</td>
<td>0.8</td>
<td>85 (0.7)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Acute exacerbation</td>
<td>76 (1.3)</td>
<td>85 (1.4)</td>
<td>0.92 (0.67–1.3)</td>
<td>0.6</td>
<td>161 (1.3)</td>
<td>13 (8)</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>5 (0.08)</td>
<td>15 (0.2)</td>
<td>0.34 (0.1–0.99)</td>
<td>0.03</td>
<td>20 (0.2)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0 (0)</td>
<td>3 (0.05)</td>
<td>0 (0–2.5)</td>
<td>0.1</td>
<td>3 (0.02)</td>
<td>0</td>
</tr>
</tbody>
</table>

*See Table 4 for expansion of abbreviations; P-Y = person-year.
†No. of patients (IR) who had each clinical presentation.
‡Comparing the incidence rate of each clinical presentation between the vaccine group and the placebo group.
§No. of patients in each clinical presentation who had influenza.
∥Significant difference.

Figure 1. Probability of not acquiring influenza-related ARI over the study year estimated by Kaplan-Meier survival analysis. Significant difference (p = 0.003 by log-rank test) comparing the probability of not acquiring influenza-related ARI between the vaccine and placebo groups.
homogeneous, including only patients with COPD, which would decrease other unknown confounders that might affect the effectiveness of influenza vaccination. The effectiveness of vaccination was consistent among patients with mild and severe airflow obstruction. The effectiveness in the patients with moderate airflow obstruction was lowest, at only 45%. This is probably explained by the smallest number of the patients in this subgroup. Bivariate analysis also supported the constant effectiveness of vaccination regardless of COPD severity, age, gender, smoking status, or comorbid diseases. However, because of the small number of the patients in the subgroup analysis, the power of the bivariate analysis to detect the potential effect modification of these factors on the effectiveness of influenza vaccination might be low.

It seemed that influenza vaccination led to a reduction in the number of influenza-related ARI at all levels of severity, including outpatient treatment, hospitalization, and mechanical ventilator use. Nevertheless, only the number of outpatient visits was significantly different between the vaccine and placebo groups. This is likely due to the smaller number of hospitalizations and mechanical ventilator use associated with influenza-related ARI. Also, there was only one death related to influenza infection; therefore, we cannot draw any conclusion regarding the risk reduction of death by influenza vaccination from this study. Also, our study showed that influenza vaccination remained effective throughout the 1-year study period. This would support the recommendation of annual influenza vaccination. The high response rates and high protection rates after the first dose vaccination with very low response rates after the second dose vaccination suggests that only one dose vaccination would be adequate for adults.

The incidence of total ARI in the vaccinated group was not different from the placebo group. This means that influenza vaccination did not prevent other ARIs unrelated to influenza virus infection. This is different from several previous reports concerning the potential effect of influenza vaccination on overall respiratory illness, including both influenza and noninfluenza respiratory illness. Most of these were observational studies performed in an influenza epidemic year. Nichol and coworkers reported that elderly patients who had been vaccinated had a reduction of approximately 30% in the rates of hospitalization for all respiratory conditions. Also, Nichol and coworkers demonstrated that in the subjects with chronic lung disease, vaccinated
subjects had a 52% reduction in hospitalization. A meta-analysis of 20 cohort studies of influenza vaccination in the elderly showed a 56% reduction in respiratory illness, and a 50% reduction in hospitalization. There are two possible explanations regarding the difference between those studies and our study. First, this study had a much smaller sample size than those large observational studies. However, if influenza vaccination could reduce the incidence and the rate of hospitalization of all respiratory illness by approximately 50% as shown in previous reports, with the incidence of ARI and the rate of hospitalization in the placebo group of 87% (55 of 63 patients had one or more ARI) and 37% (23 of 63 patients needed one or more hospitalization), respectively, at a significance level of 0.05, the sample size of this study would have a power of 99% to detect the difference in the incidence of total ARI, and 60% to detect the difference in the rate of hospitalization between the vaccine group and placebo group. Therefore, we do not think that the smaller sample size in our study was the major explanation regarding this issue. Another possible explanation that we believe to be the most likely explanation was the difference in the effect size. Most of those observational studies were done in influenza epidemic years and, therefore, the proportion of influenza-related ARI of the total ARI would be high. This would cause the effectiveness of influenza vaccination in the reduction of total ARI to be more significant than in this study, which was performed in a nonepidemic year with a lower incidence of influenza-related ARI. Therefore, the effectiveness of influenza vaccination in the prevention of overall ARI in patients with COPD would depend on how much influenza-related ARI contributes to the incidence of total ARI. This is supported by the previous two randomized controlled studies regarding influenza vaccination in patients with COPD. The first study by Howells and Tyler, which was performed in an influenza epidemic year with an incidence of influenza-related ARI of 45% of the total exacerbations, demonstrated that vaccination could significantly reduce both influenza-related exacerbation and total exacerbations of COPD. However, the study of Fell and coworkers, which was performed in an influenza nonepidemic year, demonstrated that vaccinated patients had more respiratory symptoms than control subjects.

Influenza virus infection related to approximately 8% of acute exacerbation of COPD. This infection rate was similar to the previous reports. Influenza-like illness was the most specific symptom of influenza virus infection, and influenza vaccination effectively reduced this presenting symptom in patients with COPD. Nevertheless, influenza virus infection was evidenced in only 10% of the patients with COPD who presented with influenza-like illness. Hence, clinical diagnosis of influenza is not reliable in patients with COPD.

The peak incidence of influenza infection in this study was in the rainy season, which begins in May. This is in accordance with other reports that demonstrated that in tropical regions, influenza cases occur more frequently during the rainy months instead of the winter as in the temperate regions. Influenza vaccination is recommended as the influenza activity period begins; therefore, it should be administered before May. Thus, in this study, the timing of vaccination was too late. However, the effectiveness of vaccination remained high. This may be explained by a small difference in the vaccine components between the 1996–1997 vaccine and the 1997–1998 vaccine, which only changed the influenza A (H1N1) antigen from influenza A/Texas 36/91 (H1N1) to influenza A/Johannesburg/82/96-NIB-39. Another explanation is probably the cross protection of the different subtype antibody. This implies that influenza vaccination should be administered just before the influenza activity period, but it still retains some effectiveness despite late administration.

In conclusion, influenza vaccination is highly effective in the prevention of ARI related to influenza virus infection, regardless of severity of COPD, comorbid diseases, age, gender, or current smoking status. Influenza vaccination does not prevent other ARIs unrelated to influenza. The effectiveness of influenza vaccination in the prevention of overall ARI in patients with COPD will depend on how much influenza-related ARI contributes to the incidence of total ARI. Influenza vaccination should be recommended to all patients with COPD.

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REFERENCES
8 Fauststein V, Musher DM, Cate TR. Bacterial adherence to pharyngeal cells during viral infection. J Infect Dis 1980; 141:172–176
15 Barker WH, Mullooly JP. Influenza vaccination of elderly persons: reduction in pneumonia and influenza hospitalization and deaths. JAMA 1980; 244:2547–2549