Effectiveness of Influenza Vaccine in Health Care Professionals
A Randomized Trial

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The effectiveness of influenza vaccine in reducing morbidity and mortality in children, elderly, or debilitated patients has been demonstrated in several studies.1-7 Influenza epidemics can also exact a heavy toll among younger, healthy adults.8-11 While vaccine efficacy of 70% to 90% has been documented in young adults, particularly military recruits, cost-effectiveness has not been demonstrated conclusively in this population.12-15

Since 1981, the Advisory Committee on Immunization Practices of the US Public Health Service has suggested influenza vaccine for health care professionals who care for patients at high risk for significant morbidity following influenza infection.16 Among the presumed benefits are a reduction in infection and absenteeism among health care professionals and a reduction in transmission of influenza from health care professionals to high-risk patients.12,17 Although published data support the hypothesis that infected health care professionals can serve as a vector to spread

See also pp 901 and 944 and Patient Page.
influenza among hospitalized patients, causing a variety of adverse effects from increased hospital costs to death.18,19 There are conflicting data on whether influenza vaccine decreases the rate of influenza infection or sick leave among health care professionals.20–25 However, compliance with the Advisory Committee on Immunization Practices recommendations by physicians and nurses has been poor, with rates of influenza vaccination among health care professionals reported to range from 16% to 51%.19,26,27

We undertook a prospective randomized, double-blind, controlled study to determine the benefits of influenza vaccination in young, healthy health care professionals. We assessed the effectiveness of vaccine in the reduction of serologically proven influenza infection, reported respiratory illness, and days absent from work.

METHODS

Study Population

Hospital-based physicians, nurses, and respiratory therapists from departments of pediatrics, medicine, and emergency medicine agreed to participate in the study. Subjects were eligible if they were younger than 50 years, were in good health, and were willing to report illness during the epidemic period. Exclusion criteria included history of allergic reaction to influenza vaccine or egg products, allergy to the control vaccines, pregnancy, or medical conditions that would place the subject at high risk for complications from influenza infection such as chronic pulmonary, renal, or metabolic disease, severe cardiac disease, immunosuppression, or diabetes mellitus. Informed consent was obtained from all participants. This study was approved by the Joint Committee for Clinical Investigation at the Johns Hopkins University Hospital and School of Medicine, Baltimore, Md.

Study Design and Measurements

The study was a prospective, randomized, double-blind, controlled trial conducted at the Johns Hopkins Hospital and Sinai Hospital in Baltimore (FIGURE). All vaccines and the saline placebo were administered in volumes of 0.5 mL as intramuscular injections in October and November of 1992, 1993, and 1994, with control vaccines including meningooccal vaccine, pneumococcal vaccine, or placebo, respectively.

Four-unit block randomization was used to allocate subjects to vaccine or control groups. The pharmacy was responsible for the randomization process and for labeling and dispensing vaccines and controls. The list of assignments was kept in the pharmacy until the end of the study to ensure allocation concealment. The syringes containing the vaccine or control were packaged and labeled identically and were identified only by a study number, thus keeping the assignment hidden to both subject and investigator.

A baseline blood sample was collected at the time of enrollment and vaccination in October-November, a postvaccination blood sample was drawn 1 month later to determine the serologic response to the vaccine, and a final blood sample was obtained 1 month after local influenza activity had ended to identify subjects who were infected by the influenza type A(H3N2) or type B strains during each influenza season.

Blood samples were centrifuged and frozen within 6 hours, coded, and sent to a reference laboratory for analysis. All 3 samples from each study subject were analyzed simultaneously. Hemagglutination inhibition assays were performed on all serum samples, using the appropriate influenza A(H3N2) and influenza B vaccine antigens for each annual epidemic and previously described techniques.28

At the time of enrollment and vaccination, demographic information was collected from all participants to establish their eligibility to participate. Participants were contacted by telephone 3 days after vaccination to determine the occurrence of adverse reactions. Subjects were also asked to guess which vaccine they had received but were not informed of group assignment until the code was broken after the epidemic.

Local onset of the influenza epidemic was determined through active monitoring by the hospital virology laboratory as well as through epidemiologic data obtained from local, state, and national surveys. During the influenza season, the study nurse conducted weekly telephone interviews with participants to inquire about illnesses during the previous week. Specific symptoms of respiratory illness and absences from work due to illness were recorded.

Definitions and Outcomes

Vaccine response was defined as a 4-fold increase in hemagglutination-inhibiting antibodies between the preimmunization and postimmunization specimens. Influenza infection during the yearly epidemic period was defined as a 4-fold increase in hemagglutination-inhibiting antibodies between the postimmunization and postepidemic specimens. For the purposes of this study, respiratory illness was defined as report of 2 or more of the following symptoms for 2 or more days: rhinorrhea, cough, or sore throat. Febrile respiratory illness was defined as respiratory illness with a report of fever (with or without documentation by ther-
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Vaccine effectiveness was calculated as 1−(rate in vaccine group/rate in control group). The rate ratio was also used to estimate vaccine effectiveness in reducing cumulative days of illness or absence, and the difference in rates to estimate the magnitude of vaccine effect per 100 vaccine doses.

The primary outcome was serologic evidence of infection during the influenza season; secondary outcomes included days of respiratory illness, days of febrile respiratory illness, and days absent from work due to illness.

**Statistical Analysis**

Each winter, we randomized all participants without regard to previous vaccine assignment experience. Because some study participants volunteered for more than 1 winter, our 264 volunteers were observed for a total of 361 person-winters. The vaccine strains and circulating influenza viruses were different each winter, and our data showed no effect of previous vaccine experience on protection. For these reasons, we analyzed our data as 361 subjects (person-winters); hence, several volunteers are represented for 2 or 3 winters. Comparisons between influenza vaccine recipients and controls were made on an intention-to-treat basis; influenza vaccine recipients who did not demonstrate a 4-fold increase in antibody titer after vaccination remained in the influenza vaccine group for data analysis.

Data were analyzed using STATA statistical software (STATA Corp, College Station, Tex) release 5.0 for Windows 95. The significance level chosen for all analyses was .05. A 2-sided Wilcoxon rank sum test was used to compare continuous variables between vaccine recipients and controls. Nominal or categorical variables were compared using $\chi^2$ tests of association (Yates corrected) or Fisher exact test, as appropriate. Serum titers were log transformed, and 2-sided $t$ and Wilcoxon rank sum tests were used to compare postvaccine and postinfluenza season titers among vaccine recipients and controls. Mantel-Haenszel estimates of rate ratios were used to compare the 2 groups. We estimated that at least 105 subjects were needed in each group to detect a true vaccine efficacy of 80%, assuming an $\alpha$ level of .05, power of 80%, and an influenza attack rate of 20%.

**RESULTS**

**Subject Characteristics**

A total of 264 health care professionals were studied during a 3-year period; 49 subjects participated for 2 seasons and 24 for 3 seasons. The characteristics of the study subjects are provided in Table 1. There were no differences in baseline characteristics between the influenza vaccine recipients and the control recipients. Fifty-seven percent of the participants were women. Eighty-six percent of participants were white, 4% were black, 9% were Asian/Pacific Islander, and 1% were Hispanic. Resident physicians represented 75% of the study population, 2% were attending physicians, 18% were nurses, and 5% were medical students and respiratory therapists.

**Vaccines and Surveillance**

Influenza vaccine components are shown in Table 2. Because some subjects participated for more than 1 winter season, control vaccines were changed each year. To encourage study participation, we used vaccines with proven benefit for the control subjects for the first 2 years. The surveillance during the 3 winter periods included 361 person-winters or 4746 person-weeks of illness surveillance. Clinical follow-up was obtained for all subjects. Serologic data were obtained for 99.4% of the subjects, including 180 vaccine recipients and 179 control recipients, for 359 person-winters of serologic surveillance.

There were no absences due to vaccine adverse effects during the observation period 3 days after vaccination. Three significant adverse events were attributed to study participation, 1 case each of serum sickness and cellulitis in recipients of meningococcal vaccine and 1 case of lymphangitis in a saline-control recipient. Other than mild pain or swelling at the injection site, the rest of the subjects reported no significant adverse effects.

Three days after receipt of vaccine or control, subjects were asked about adverse effects. They were also asked to guess whether they had received influenza vaccine or control. Successful masking of subjects was achieved in 2 of 3 years. Subjects in the first 2 seasons could not predict their correct vaccine assignment ($\kappa = -0.19, -0.05$, respectively; $P>0.69$ for both years). However, saline-control recipients in 1994-1995 did predict their correct assignment at a statistically significant rate ($\kappa = 0.32, P<0.01$).

National and local virology labs reported influenza A(H3N2) in substantial numbers in all 3 years, type B was active

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**Table 1. Influenza Vaccine Study Subject Characteristics**

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Influenza Vaccine</strong> (n = 52)</td>
<td>Meningococcal Vaccine† (n = 50)</td>
<td><strong>P</strong></td>
<td>Influenza Vaccine (n = 51)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>28.4 (2.6)</td>
<td>28.9 (2.8)</td>
<td>.28</td>
</tr>
<tr>
<td>Male sex</td>
<td>52</td>
<td>50</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Prior year influenza immunization</td>
<td>42</td>
<td>32</td>
<td>.38</td>
</tr>
<tr>
<td>Current smoker</td>
<td>2</td>
<td>4</td>
<td>.61</td>
</tr>
<tr>
<td>Children at home</td>
<td>8</td>
<td>18</td>
<td>.21</td>
</tr>
</tbody>
</table>

*Data are presented as percentages except where noted otherwise.
†Control vaccines used for each winter season.
in 2 years, and A(H1N1) was essentially absent. A good match was achieved between the epidemic influenza subtypes and the vaccine components in year 2 of the study. There was a partial match in years 1 and 3 (Table 2).

Effectiveness

Vaccine response to influenza A(H3N2), measured by a 4-fold increase in hemagglutination inhibition titers after vaccination was demonstrated in 4% to 78% of subjects and to influenza B in 33% to 52% of subjects. Overall, vaccine response was noted in 57% of subjects for A(H3N2) and in 40% of subjects for influenza B.

The number and rate of influenza type A and B infection in study subjects each year is shown in Table 3. The rate of influenza A(H3N2) infection per 100 person-winters was 1.1 in influenza vaccinees and 8.9 in controls, for an effectiveness of 88% (95% confidence interval [CI], 47%-97%; P = .001). The rate of influenza type B infection per 100 person-winters was 0.6 in influenza vaccinees and 5.0 in controls, for an effectiveness of 89% (95% CI, 14%-99%; P = .02).

Overall incidence of influenza infection was 1.7% among vaccine recipients vs 13.9% among controls.

Only 1 (2.3%) of 43 consecutive year influenza vaccine recipients became infected with influenza compared with 2 (1.5%) of 138 receiving the vaccine for the first time. Control subjects who had received the vaccine during the previous season were infected at the same rate (15%) as controls who had not been vaccinated during the prior year (13.6%).

Among the 179 unvaccinated subjects with serologic evidence of infection with influenza A or B (n = 24, 13.3%) were more likely than those without evidence of infection (n = 155) to have febrile respiratory illness (58% vs 14%, respectively; P < .001), had longer mean duration of febrile respiratory illness (1.67 vs 0.20 days; P < .001), had absence from work (29% vs 7.7% of subjects; P = .006), and had higher mean number of days absent (0.67 vs 0.14 days; P = .001). The definition of febrile respiratory illness used in this study had a sensitivity of .58, specificity of .86, and positive predictive value of .37 for influenza infections. The mean number of reported febrile days actually exceeded the mean number of absence days, suggesting that these health care professionals reported for work during febrile respiratory illnesses. In contrast to control subjects, none of the 3 persons vaccinated for influenza who were infected reported any febrile respiratory illness or work absence.

The estimates of clinical effectiveness of influenza immunization are based on 264 subjects over 361 person-winters. Most subjects had no days of illness or work absence; the range for absence was 0 to 7 days per subject. The mean absence from work for the vaccinated group was 0.1 days (SD, 0.35) and for the control group, it was 0.21 days (SD, 0.75). The median absence for both groups was 0 days. The mean febrile respiratory illness for the vaccinated group was 0.29 days (SD, 0.68) and for the control group, it was 0.41 days (SD, 1.0). The median absence due to febrile respiratory illness was 0 days for both groups. Subjects who were vaccinated (n = 181) had fewer cumulative days of febrile respiratory illness than controls (n = 180) (52 days [28.7 days per 100 subjects] vs 73 days [40.6 days per 100 subjects], respectively; P = .57, Mantel-Haenszel test). The observed 29% reduction (95% CI, −22% to 59%) was not statistically significant. Subjects in the vaccinated group also had fewer cumulative days of work absence than those in the control group (18 days [9.9 days per 100 subjects] vs 38 days [21.1 days per 100 subjects]; P = .41, Mantel-Haenszel test). The observed 53% reduction (95% CI, −56% to 86%) was not statistically significant.

**Table 2. Characteristics of Study Vaccines and Epidemic Influenza Viruses (1992-1995)**

<table>
<thead>
<tr>
<th>Season</th>
<th>脯 uninfluenza A(h3n2), No. (%)</th>
<th>脨 uninfluenza B, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992-1993</td>
<td>A/Texas/36/91 (H1N1) 1</td>
<td>A/Texas/36/91</td>
</tr>
<tr>
<td></td>
<td>A/Beijing/353/89 (H3N2) 30</td>
<td>A/Beijing/32/92</td>
</tr>
<tr>
<td></td>
<td>B/Panama/45/90 69</td>
<td>B/Panama/45/90</td>
</tr>
<tr>
<td>1993-1994</td>
<td>A/Texas/36/91 (H1N1) 0</td>
<td>A/Texas/36/91</td>
</tr>
<tr>
<td></td>
<td>A/Beijing/32/92 (H3N2) 98</td>
<td>A/Beijing/32/92</td>
</tr>
<tr>
<td></td>
<td>B/Panama/45/90 2</td>
<td>B/Panama/45/90</td>
</tr>
<tr>
<td>1994-1995</td>
<td>A/Texas/36/91 (H1N1) 1</td>
<td>A/Texas/36/91</td>
</tr>
<tr>
<td></td>
<td>A/Shangdong/9/93 (H3N2) 61</td>
<td>A/Shangdong/09/93‡</td>
</tr>
<tr>
<td></td>
<td>B/Panama/45/90 38</td>
<td>B/Panama/45/90‡</td>
</tr>
<tr>
<td></td>
<td>B/Beijing/184/93§</td>
<td>B/Beijing/184/93§</td>
</tr>
</tbody>
</table>

*Data are presented as type/geographic origin/laboratory strain number, and year of isolation. Control vaccines were meningococcal vaccine in 1992-1993, pneumococcal vaccine in 1993-1994, and saline placebo in 1994-1995.
†Data reported to Centers for Disease Control and Prevention from south Atlantic region. (N. Cox, MD, personal communication, 1998.)
‡Sixty-four percent of the strains were A/Shangdong/09/93, and 36% were A/Johannesburg/33/94.
§Twenty-five percent of the strains were B/Panama/45/90, and 75% were B/Beijing/184/93.

**Table 3. Influenza Infection During Annual Epidemics, 1992-1995***

<table>
<thead>
<tr>
<th>Year of Study</th>
<th>Influenza A(H3N2), No. (%)</th>
<th>Influenza B, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992-1993</td>
<td>2/52 (3.9)</td>
<td>0/52 (0)</td>
</tr>
<tr>
<td>1993-1994</td>
<td>0/51 (0)</td>
<td>0/52 (0)</td>
</tr>
<tr>
<td>1994-1995</td>
<td>0/77 (0)</td>
<td>1/77 (1.3)</td>
</tr>
<tr>
<td>Total 1992-1995</td>
<td>2/180 (1.1)</td>
<td>1/180 (0.6)</td>
</tr>
</tbody>
</table>

*Data are presented as type/geographic origin/laboratory strain number, and year of isolation. Control vaccines were meningococcal vaccine in 1992-1993, pneumococcal vaccine in 1993-1994, and saline placebo in 1994-1995.
†Data reported to Centers for Disease Control and Prevention from south Atlantic region. (N. Cox, MD, personal communication, 1998.)
‡Sixty-four percent of the strains were A/Shangdong/09/93, and 36% were A/Johannesburg/33/94.
§Twenty-five percent of the strains were B/Panama/45/90, and 75% were B/Beijing/184/93.

**COMMENT**

The results from this 3-year study of health care professionals indicate that influenza
vaccine is effective in preventing infection and may help to reduce cumulative days absent from work during the influenza epidemic. To our knowledge, ours is the first study of health care professionals to assess the effect of influenza vaccine in a randomized, double-blind, controlled trial over 3 successive epidemic seasons. We used results of serological studies to assess response to vaccine, to document infection by influenza A(H3N2) or B, and to define the association of our clinical outcome with objective data on infection. We closely monitored illness by directly contacting study participants by telephone each week during the influenza season and achieved 100% clinical and 99.4% serological follow-up. Our overall vaccine effectiveness of 88% is similar to results from previous studies in young adults.14,30 as is the cumulative influenza attack rate of 14% in controls.8,31,32 The variation in matching between the vaccine and the epidemic influenza strains for each of the 3 years suggests our effectiveness estimates are generalizable to programs of annual vaccination during periods of antigenic drift.

Prior studies in healthy adults have shown a decreased rate of absence from work among those vaccinated with influenza vaccine.13,33 In a randomized controlled trial of healthy adults, Nichol et al13 showed a 0.5-day reduction in absenteeism during a study period with an unusually high apparent influenza attack rate.32 Studies conducted specifically among health care professionals have shown mixed results with regard to work absence.22,23,25 The health care professionals in our study seem unlikely to be absent from work even when they experience a febrile respiratory illness, a characteristic that may differ from that of the general adult working population. Although the rates of work absence in the health care professionals in our group are only one third of those of working adults in the study by Nichol et al (+1 days vs 122 days per 100 subjects, respectively), the 2 studies show similar estimates of effectiveness of influenza vaccine in reducing cumulative work absence (53% and 43%, respectively).13 Direct comparison of respiratory illness experience in the 2 studies is not possible because our definition included fever, which was not required in the definition made by Nichol et al. However, the estimated influenza vaccine effectiveness against either clinical definition was similar: 29% in our study and 35% in the study by Nichol et al. Although similar to other studies, the point estimates in our subjects do not reach statistically significant levels; a larger study is needed to confirm these estimates.

Our data show a 14% risk of developing influenza type A or B infection for the individual health care professional who remains unvaccinated and show that influenza infection will increase the risk of experiencing a febrile respiratory illness or work absence by 4-fold. Moreover, among subjects in our study, influenza infection was associated with experiencing an additional 1.5 days of febrile respiratory illness and 0.5 days of absence from work during each influenza season. Our data also provide a point estimate of an absolute vaccine effect of 11 work absence days that were averted per 100 vaccinated and confirm the relative effect of 88% reduction in infection.

One criticism of annual influenza vaccination for young, healthy adults is that it may be counterproductive, both in the short-term and in the long-term.34 Data from a study of British schoolboys vaccinated in 3 consecutive years in the 1970s suggested there was less protection from influenza infection, as defined by either culture or serological results, if the vaccine had been received the previous year.35 In 1983, Gill and Murphy36 showed that previous infection conferred long-term immunity to the homologous influenza virus; subjects who had been alive during the previous H1N1 epidemics of 1947-1957 had a lower attack rate than subjects exposed to H1N1 for the first time when it reappeared in 1977. Subsequent studies have shown that while 4-fold seroconversion to the vaccine components is much lower among subjects who have been vaccinated in prior years, effectiveness in preventing culture or serologically proven infection was better after repeated annual vaccination.14,15 In a matched case-control study. Ahmed et al37 showed a reduction in mortality in an elderly population for those who had received repeated annual vaccination compared with a single-season vaccination.

Sixty-five percent of the subjects in our study who did not have a history of influenza vaccination in the previous year seroconverted to the H3N2 component after vaccination, whereas only 30% of those receiving the vaccine for the second consecutive year seroconverted. These rates are consistent with the previous studies.14,15 However, protection within those groups was equivalent; we found no significant influenza vaccine carryover effect.

The influenza infection rate in influenza vaccine recipients and in controls was not altered by the vaccine experience in the previous year, which supports the recommendation for yearly influenza vaccination. Although we did not study it, nosocomial influenza infection has been well documented as a cause of increased hospital days and mortality among inpatients.11,38-40 Influenza infection in 10% to 20% of a hospital staff per season has major implications for nosocomial transmission, particularly given prolonged shedding of the virus from infected persons.41 Two recent studies have shown a reduction in nosocomial infection after large-scale vaccination of health care professionals, including a 1997 study that showed a decrease in total mortality rates from 17% to 10% among nursing home patients.42,43 These facts, coupled with our data showing that hospital employees report to work despite having a febrile illness, lend support to institutional efforts to vaccinate health care professionals.

Our study has several limitations. First, previous studies have shown that serological analysis may fail to detect up to 20% to 30% of culture-proven cases of influenza infection in adults.15,44 We may not have detected all influenza infections, although it is not clear if this effect is likely to be greater in the influenza vaccine group or the control group. Analysis of serologic response using the adjustment suggested by Govaert et al1 did not increase the number of infec-
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In conclusion, influenza vaccine is effective in preventing serologically proven influenza infection in young, healthy hospital-based health care professionals and may reduce cumulative days of illness and absence. These data suggest that a policy of annual immunization with influenza vaccine in health care professionals will reduce influenza infections and can reduce associated illness.

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REFERENCES


