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THE EFFECTIVENESS OF VACCINATION AGAINST INFLUENZA IN HEALTHY, WORKING ADULTS

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Abstract Background. Although influenza causes substantial morbidity and mortality in all age groups, current recommendations emphasize annual immunization for people at high risk for complications of influenza. We conducted a double-blind, placebo-controlled trial of vaccination against influenza in healthy, working adults.

Methods. In the fall of 1994, we recruited working adults from 18 to 64 years of age from in and around the Minneapolis–St. Paul area and randomly assigned them to receive either influenza vaccine or placebo injections. The primary study outcomes included upper respiratory illnesses, absenteeism from work because of upper respiratory illnesses, and visits to physicians' offices for upper respiratory illnesses. The economic benefits of vaccination were analyzed by estimating the direct and indirect costs associated with immunization and with upper respiratory illnesses.

Results. We enrolled a total of 849 subjects. Baseline characteristics were similar in the two groups. During the follow-up period, consisting of the 1994–1995 influenza season (December 1, 1994, through March 31, 1995), those who received the vaccine reported 25 percent fewer episodes of upper respiratory illness than those who received the placebo (105 vs. 140 episodes per 100 subjects, $P < 0.001$), 43 percent fewer days of sick leave from work due to upper respiratory illness (70 vs. 122 days per 100 subjects, $P = 0.001$), and 44 percent fewer visits to physicians' offices for upper respiratory illnesses (31 vs. 55 visits per 100 subjects, $P = 0.004$). The cost savings were estimated to be \$46.85 per person vaccinated.

Conclusions. Vaccination against influenza has substantial health-related and economic benefits for healthy, working adults. (N Engl J Med 1995;333:889-93.)

ALTHOUGH most deaths from influenza occur among elderly people, all age groups are affected by this illness. Annual attack rates average 10 to 20 percent and are higher during severe epidemics.¹ Symptoms include the abrupt onset of fever, myalgia, sore throat, nonproductive cough, headache, and malaise. Influenza is sometimes associated with malaise persisting for several weeks and often results in restriction of activity.² Influenza accounts for millions of days lost from work each year.³

The current recommendations of the Advisory Committee on Immunization Practices target persons at increased risk for complications of influenza for annual immunization, although all people who wish to avoid illness are encouraged to consider vaccination.⁴ We undertook this trial to clarify the benefits of immunization in a population not at high risk for complications. The

effects of vaccination on the frequency of upper respiratory illness, sick leave from work, and use of health care services were assessed in healthy, working adults.

METHODS

Subjects

Subjects were recruited from the Minneapolis–St. Paul area through advertisements at work sites and in local newspapers and through recruitment sessions at shopping malls. People were eligible if they were 18 to 64 years old, were employed full-time, and had no medical conditions, such as chronic cardiopulmonary disease, diabetes mellitus, or other serious medical conditions, that would place them at high risk for complications of influenza. The criteria for exclusion were a history of immediate hypersensitivity reactions to eggs (because the vaccine may contain small amounts of residual egg protein), thimerosal (a preservative in the vaccine), or previous vaccination against influenza, and pregnancy or planned pregnancy within three months. Informed consent was obtained from all participants. The study was approved by the Human Studies Committee of the Minneapolis Veterans Affairs Medical Center.

Study Design and Data Collection

The study was a randomized, double-blind, placebo-controlled trial. Subjects received injections of vaccine (trivalent split-virion influenza vaccine containing 15 μg of antigen from the component strains A/Texas/36/91, A/Shangdong/9/93, and B/Panama/45/90; Fluzone, Connaught Laboratories, Swiftwater, Pa.) or placebo (vaccine diluent) according to a computer-generated randomization schedule. Ten-unit

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blocks were used to ensure balanced allocation of subjects to the two groups. Accountability logs in which investigators documented subjects' group assignments were completed to ensure adherence to the randomization schedule. Vaccine and placebo were available in pre-loaded syringes that were identical in appearance and labeled only with the study code. Blinding was maintained until all study data were collected.

Base-line data on demographic and health-related characteristics were collected by means of a questionnaire administered at the time of enrollment. Follow-up data were obtained through structured telephone interviews. Most telephone surveys were conducted with a computerized, interactive-response telecommunication system (Posit, Health Outcomes Technologies, Doylestown, Pa.). Subjects who required assistance were interviewed by an operator. Five interviews were completed during the follow-up period. The first call was initiated 7 to 14 days after the study injection to collect information on side effects during the week after the injection, and the second through fifth calls were made during January, February, March, and April to identify occurrences of upper respiratory illness, use of sick leave, and visits to physicians' offices in the preceding month. Subjects were also encouraged to record information about these outcomes in "illness logs" and were asked to refer to the logs during their follow-up interviews. During the final interview, subjects were also asked whether they had received an influenza vaccination in addition to the study injection at any time during the study and which study injection they thought they had received.

Study Outcomes and Statistical Analysis

An upper respiratory illness was defined as a sore throat associated with either a fever or a cough that lasted at least 24 hours. On the basis of previous experience with influenza seasons in Minnesota, the follow-up period was defined as December 1, 1994, through March 31, 1995 (the influenza season). The primary outcomes were the totals during four months for episodes of upper respiratory illness, days of work lost because of respiratory illness, and visits to physicians' offices for respiratory illness. Secondary outcomes included the proportion of subjects with any upper respiratory illness, days of respiratory illness, days of work lost because of all illnesses, and estimates of the economic benefits associated with vaccination. Information was also collected on side effects during the week after the study injection.

Bivariate analyses to compare vaccine and placebo recipients included chi-square tests for categorical variables and Student's *t*-tests for continuous variables. The kappa statistic was used to assess the adequacy and maintenance of blinding.⁵ The effectiveness of the vaccine was calculated as follows: [(rate of the outcome variable in placebo recipients - rate in vaccine recipients)/rate in placebo recipients] × 100 percent. All statistical tests were performed with SPSS 6.1 for Windows software (SPSS, Chicago).

Estimates of the economic benefits of vaccination were based on the primary study outcomes of sick leave and visits to physicians' offices related to respiratory illness. Costs were calculated from the social perspective as combined direct and indirect costs, as follows⁶: net costs = direct costs + indirect costs; direct costs = costs of vaccination + costs of medical care for side effects - costs of medical care for disease averted; indirect costs = costs of work time lost for vaccination + costs of work loss due to side effects - costs of work loss averted.

The numbers of visits to physicians' offices and days of work lost that were avoided because of vaccination were taken from the point estimates for the primary study outcomes. A vaccination was estimated to take 30 minutes of work time and cost \$10, on the basis of a survey of public and work-site immunization programs (Nichol KL: unpublished data). The estimate of two days of work lost per 100 vaccinations because of side effects of the vaccine was based on the observed, though statistically nonsignificant, differences between vaccine and placebo recipients during the week after the study injection. We estimated that half the people with side effects would see a physician. Work-loss costs were estimated at \$93.40 per day, based on the 1994 median weekly earnings of full-time U.S. workers.⁷ The cost for a visit to a physician's office was estimated to be \$69.51, on the basis of the mean fee for a visit to a physician's office for an established patient in the 1994 American Medical Association Socioeconomic Mon-

itoring System Core Survey,⁸ a list of diagnostic tests and medications associated with visits to physicians for upper respiratory illnesses from the 1992 National Ambulatory Medical Care Survey of the National Center for Health Statistics, payments to physicians for diagnostic tests from the 1993 Physician Payment Review Commission Multipayer Database, and the costs of generic medications for the treatment of upper respiratory illnesses in a survey of three local branches of national franchise pharmacies (Nichol KL: unpublished data). All costs were adjusted to 1994 dollars with use of the Consumer Price Index. More detailed explanations of these estimates are available elsewhere.*

Sample-size calculations were based on the expected proportions of subjects with respiratory illnesses. For an event rate of 50 percent in the placebo group with 30 percent of these events being due to influenza (two-sided alpha, 0.05; beta, 0.20), at least 410 subjects per group were needed to enable us to detect differences, assuming a vaccine efficacy of 70 percent. Sample-size calculations were performed with Power software (Epicenter Software, Pasadena, Calif.).

RESULTS

A total of 849 subjects were enrolled between October 10 and November 30, 1994. The characteristics of the subjects according to treatment assignment are shown in Table 1. Randomization resulted in an even distribution of all base-line measures, including characteristics that might be independently related to the study outcomes, such as health status, number of children in the household, smoking status, and sick leave during the past six months.

After enrollment, 3 subjects were dropped from the study because of incorrect addresses and telephone numbers, leaving 424 placebo and 422 vaccine recipients. Follow-up interviews to ascertain side effects were completed for 841 subjects (99 percent). There were no significant differences between vaccine and placebo recipients with regard to specific systemic symptoms, although vaccine recipients were more likely to report local symptoms (Table 2). The mean number of days of sick leave during the week following the injection was 4.5 per 100 for the placebo recipients and 6.5 per 100 for the vaccine recipients ($P=0.34$).

After the interview focusing on side effects, five additional subjects were withdrawn. The reasons included a refusal to continue with the study (two subjects in the vaccine group) and incorrect addresses or telephone numbers (two subjects in the placebo group and one in the vaccine group). Complete follow-up data were obtained for 416 of 422 placebo recipients (99 percent) and 409 of 419 vaccine recipients (98 percent; $P=0.44$).

During the study period, 69 percent of the placebo recipients and 61 percent of the vaccine recipients had at least one upper respiratory illness ($P=0.018$). Cumulative rates of respiratory illness, sick leave, and visits to physicians' offices for respiratory illnesses and associated rates of vaccine effectiveness are summarized in Table 3. For each outcome, vaccination was associated with significantly fewer events, with the greatest re-

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Table 1. Base-Line Characteristics of the Study Subjects.*

CHARACTERISTIC	PLACEBO GROUP (N = 425)	VACCINE GROUP (N = 424)	P VALUE
Mean age (yr)	39.9	39.2	0.27
Female sex (%)	66.4	60.2	0.07
Education (%)			0.68
10–12 yr	5.2	5.0	
High-school graduate	15.5	14.9	
College	40.7	44.8	
Other	38.6	35.3	
Marital status (%)			0.43
Married	63.7	66.7	
Divorced	11.3	8.7	
Single	21.5	22.2	
Other	3.5	2.4	
Annual income (%)			0.34
<\$20,000	16.4	17.2	
\$20,000–\$39,000	49.3	44.3	
>\$39,000	34.3	38.5	
Mean no. of persons in household	3.0	2.9	0.48
Child in day care (% of subjects)	18.5	19.7	0.73
Child in school (% of subjects)	45.8	44.9	0.84
Health status (%)			0.70
Excellent	54.2	55.5	
Good	44.1	43.4	
Fair	1.7	1.2	
Cigarette-smoking status (%)			0.47
Current smoker	13.4	13.1	
Former smoker	32.3	28.7	
Never smoked	54.2	58.2	
Household exposure to cigarette smoke (%)	19.1	17.0	0.44
Sick leave during previous 6 mo (%)	40.9	35.6	0.13
No prior influenza vaccination (%)	76.6	74.0	0.53

*Because of rounding, percentages do not always total 100.

ductions in the more severe outcomes: days of work lost and visits to physicians' offices.

The original treatment assignments were well maintained throughout the study. Only one person in the placebo group (0.2 percent) and two in the vaccine group (0.5 percent) received influenza vaccine from another source. Blinding was also well maintained. When asked during the final interview which type of injection they thought they had received, only 60.3 percent of the placebo recipients and 54.3 percent of the vaccine recipients correctly identified their injection, with an overall rate of agreement of 57 percent. This correlated with a kappa of 0.15, indicating agreement only slightly better than would have resulted from chance alone.

The results of the economic analysis are shown in Table 4. On the basis of the outcomes observed in the trial, direct savings in medical costs were estimated to be \$5.99 per person vaccinated (\$599 per 100 persons), and indirect cost savings were estimated to be \$40.86 per person vaccinated (\$4,086 per 100 persons). Combined cost savings were estimated to be \$46.85 per person vaccinated (\$4,685 per 100 persons).

DISCUSSION

The results of this placebo-controlled trial show the benefits that vaccination against influenza offers for healthy, working adults. Immunization decreased the frequency of upper respiratory illnesses by 25 percent, absenteeism from work due to upper respiratory illness by 43 percent, absenteeism due to all illnesses by 36 percent, and visits to physicians' offices for upper res-

piratory illness by 44 percent. On the basis of the observed decreases in sick leave and visits to physicians for upper respiratory illness, we estimate that vaccination was associated with cost savings of \$46.85 per person vaccinated.

Previous studies of the clinical effectiveness of the influenza vaccine in working adults have had varying results. Trials in the 1950s and 1960s in the United Kingdom,^{9–11} United States,¹² and Australia,¹³ using early monovalent or bivalent formulations of the vaccine, demonstrated a reduction in absenteeism during some but not all influenza seasons. The years in which the vaccine was found to be ineffective were generally those in which there was a poor match between the virus strains in the vaccine and circulating strains. A five-year study in the early 1970s among postal workers in the United Kingdom also suggested benefit.¹⁴ The findings of that study, however, are unreliable because of base-line differences in absenteeism between the intervention and control groups. More recent trials in the United States have confirmed the efficacy of the vaccine among healthy adults, as indicated by the frequency of laboratory-confirmed infection.^{15,16} In one study, rates of clinical illness were also decreased,¹⁶ but absenteeism from work was not evaluated. Another recent trial that assessed rates of clinical illness and absenteeism failed to demonstrate a benefit.¹⁷ That study had a small sample, however. Furthermore, during the 1985–1986 study year, there was a poor match between the vaccine strains and circulating viruses.

The present study extends these observations. Our trial had a sample of adequate size; the study year was characterized by an excellent match between the strains in the vaccine and the predominant circulating virus strains, as has been the case for seven of the past nine years (Cox N, Centers for Disease Control and Prevention: personal communication); and we evaluated a broad range of outcomes including clinical illness, absenteeism from work, use of health care services, and economic benefits.

The benefits observed in this study probably represent a low-to-intermediate estimate of the benefits that might be seen in other years. Influenza activity was at low-to-moderate levels in Minnesota in 1994–1995.¹⁸ During seasons with higher levels of activity, such as

Table 2. Side Effects Associated with Vaccination.*

SYMPTOM	PLACEBO GROUP	VACCINE GROUP	P VALUE
	percent		
Fever	6.1	6.2	0.96
Tiredness	19.4	18.9	0.93
Feeling "under the weather"	17.5	16.0	0.63
Muscle aches	5.7	6.2	0.84
Headaches	14.4	10.8	0.14
Arm soreness	24.1	63.8	<0.001

*The data represent the proportions of subjects who reported having the symptom during the seven days after the study injection.

years when there are severe epidemics, the benefits of vaccination would undoubtedly be greater.

Our study was not designed to detect differences between vaccine and placebo recipients with regard to serious complications of influenza, including hospitalization and death. Influenza epidemics are, however, associated with increased rates of hospitalization for acute respiratory disease in all age groups.¹⁹⁻²¹ Furthermore, influenza — together with pneumonia — accounts for 6000 to 7000 deaths each year among persons 18 to 64 years of age.^{22,23} A substantial proportion of these deaths probably represent mortality associated with influenza epidemics.²¹ Vaccination against influenza markedly decreases the numbers of hospitalizations and deaths due to complications of influenza among the elderly.²⁴⁻²⁷ It is probable that vaccination is of similar benefit in younger persons.

In our study, vaccination was associated not only with a reduction in days of work lost because of upper respiratory illness but also with a reduction in absenteeism due to all illnesses. Upper respiratory infections accounted for approximately 65 percent of sick-leave days during the study period. Because only half the people with influenza have classic symptoms,¹ it is likely that some subjects with influenza did not have upper respiratory symptoms. This would have resulted in a misclassification of their illnesses into a non-upper-respiratory category. Episodes of influenza may also have predisposed subjects to secondary illnesses.

Vaccination of the elderly against influenza clearly saves money.^{3,26-28} Analyses of the influenza vaccine in healthy, younger adults also suggest that vaccination is cost effective and possibly cost saving.^{3,29-31} Our estimates of direct and indirect cost savings corroborate these findings and indicate that the economic benefits of vaccinating working adults may be greater than previously estimated. Our figures may underestimate the actual savings associated with vaccination in this population for several reasons. We did not, for example, include in our analysis savings associated with decreases in nonrespiratory illnesses or decreases in the rates of

Table 4. Economic Benefits Associated with Vaccination.

OUTCOME VARIABLE	COSTS (SAVINGS) PER 100 SUBJECTS (1994 DOLLARS)
Direct costs	
Vaccination (\$10 per vaccination)*	1,000.00
Medical care for side effects (1 office visit per 100 subjects)†‡	69.51
Medical care avoided (24 office visits for upper respiratory illness per 100 subjects)†§	(1,668.24)
<i>Total direct savings</i>	<i>(598.73)</i>
Indirect costs	
Work time lost for vaccination (30 min per vaccination = 50 hours per 100 subjects)*¶	583.75
Work loss due to side effects (2 days per 100 subjects)‡¶	186.80
Work loss avoided (52 days for upper respiratory illness per 100 subjects)§¶	(4,856.80)
<i>Total indirect savings</i>	<i>(4,086.25)</i>
Net savings	(4,684.98)

*A single vaccination was estimated to take 30 minutes of work time and to cost \$10, on the basis of a survey of public influenza-vaccination clinics and a local work-site vaccination program.

†A visit to a physician's office, including diagnostic tests and medications, was estimated to cost \$69.51, as described in the Methods section.

‡Given the observed though statistically nonsignificant differences between vaccine and placebo recipients, side effects of the vaccine were estimated to result in an additional two days of sick leave per 100 subjects vaccinated, with half of these (one per 100) resulting in a visit to a physician.

§The numbers of days of sick leave and visits to physicians' offices that were avoided are from Table 3.

¶Costs of work lost were estimated at \$93.40 per day, on the basis of the 1994 median weekly earnings (\$467) of full-time U.S. workers.⁷

hospitalization and death due to influenza and its complications. The economic benefits for a particular population depend, of course, on the actual costs of illness in that population, the type and severity of influenza, the clinical attack rate, and the effectiveness of the vaccine during the season in question.

Concern about side effects is a barrier to immunization. Two recent trials have shown that the vaccination of elderly people against influenza is not associated with higher rates of systemic side effects than placebo injections.^{32,33} In our study we observed virtually identical results among younger, low-risk subjects.

We relied on subjects' own reports as the measure of clinical outcomes in this study. Such reports of sick leave have been shown to be reliable and accurate.³⁴ In our study, we minimized the recall period (and the possibility of recall bias) for subjects by conducting monthly follow-up interviews. Blinding was also well maintained despite the higher rate of local reactions among vaccine recipients. Therefore, the subjects' reports of outcomes should have provided a valid and unbiased estimate of the effects of vaccination in the study.

The group of participants in this study was broadly representative of the general population. Exclusion criteria were kept to a minimum, re-

Table 3. Health-Related Benefits Associated with Vaccination.*

STUDY OUTCOME	RATE PER 100 SUBJECTS		DIFFERENCE (95% CI)	VACCINE EFFECTIVENESS	P VALUE
	PLACEBO GROUP	VACCINE GROUP			
Primary					
Episodes of upper respiratory illness	140	105	35 (17-53)	25	<0.001
Days of sick leave due to upper respiratory illness	122	70	52 (21-84)	43	0.001
Visits to physicians' offices for upper respiratory illness	55	31	24 (8-40)	44	0.004
Secondary					
Days of upper respiratory illness	974	780	194 (15-373)	20	0.034
Days of sick leave due to all illnesses	203	129	74 (23-125)	36	0.004

*The values are mean cumulative totals for the four-month period from December 1, 1994, through March 31, 1995 (the influenza season). CI denotes confidence interval. Vaccine effectiveness was calculated as the difference in the rates of outcome variables (placebo group - vaccine group) divided by the rate in the placebo group, multiplied by 100.

cruitment was conducted in a variety of settings, and participation was made as convenient as possible. The results of this study should therefore be generalizable to other working adults and have important implications for the 87 million full-time workers in the United States.⁷

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