Effectiveness and Cost-Benefit of Influenza Vaccination of Healthy Working Adults

A Randomized Controlled Trial

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Context Although the cost-effectiveness and cost-benefit of influenza vaccination are well established for persons aged 65 years or older, the benefits for healthy adults younger than 65 years are less clear.

Objective To evaluate the effectiveness and cost-benefit of influenza vaccine in preventing influenzalike illness (ILI) and reducing societal costs of ILI among healthy working adults.

Design Double-blind, randomized, placebo-controlled trial conducted during 2 influenza seasons.

Setting and Participants Healthy adults aged 18 to 64 years and employed full-time by a US manufacturing company (for 1997-1998 season, n=1184; for 1998-1999 season, n=1191).

Interventions For each season, participants were randomly assigned to receive either trivalent inactivated influenza vaccine (n=595 in 1997-1998 and n=587 in 1998-1999) or sterile saline injection (placebo; n=589 in 1997-1998 and n=604 in 1998-1999). Participants in 1997-1998 were rerandomized if they participated in 1998-1999.

Main Outcome Measures Influenzalike illnesses and associated physician visits and work absenteeism reported in biweekly questionnaires by all participants, and serologically confirmed influenza illness among 23% of participants in each year (n=275 in 1997-1998; n=278 in 1998-1999); societal cost of ILI per vaccinated vs unvaccinated person.

Results For 1997-1998 and 1998-1999, respectively, 95% (1130/1184) and 99% (1178/1191) of participants had complete follow-up, and 23% in each year had serologic testing. In 1997-1998, when the vaccine virus differed from the predominant circulating viruses, vaccine efficacy against serologically confirmed influenza illness was 50% (P=.33). In this season, vaccination did not reduce ILI, physician visits, or lost workdays; the net societal cost was $65.59 per person compared with no vaccination. In 1998-1999, the vaccine and predominant circulating viruses were well matched. Vaccine efficacy was 86% (P=.001), and vaccination reduced ILI, physician visits, and lost workdays by 34%, 42%, and 32%, respectively. However, vaccination resulted in a net societal cost of $11.17 per person compared with no vaccination.

Conclusion Influenza vaccination of healthy working adults younger than 65 years can reduce the rates of ILI, lost workdays, and physician visits during years when the vaccine and circulating viruses are similar, but vaccination may not provide overall economic benefits in most years.

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THE COST-EFFECTIVENESS OF INactivated influenza vaccination in reducing influenza illness, hospitalization, and death is well established in persons aged 65 years or older, a group that is at increased risk of severe influenza-related complications.[1-5] However, the benefits of annual influenza vaccination of healthy adults younger than 65 years are less clear.[5-12] Between 1% and 26% of persons aged 18 to 64 years may be infected with influenza annually,[13-18] and the associated work absenteeism can result in substantial societal costs.[5,6,9,11,19-21] To date, only 1 randomized, placebo-controlled cost-effectiveness study among healthy working adults has been published.[6] That study, conducted from the societal perspective, reported a net savings of $46.85 per healthy adult worker vaccinated against influenza. However, other studies of non–high-risk adults have not shown similar economic benefits or similarly high attack rates of influenza-attributable illness.[5,12-18] Most influenza vaccine studies of healthy working adults have been

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conducted during a single influenza season,[6,10,11,19-22] limiting their generalizability because influenza illness rates and vaccine efficacy may differ substantially from year to year. In addition, other studies of influenza vaccination of healthy adults have not included laboratory confirmation of influenza illness.[6,9-11] Laboratory testing to support epidemiologic findings is important because the specificity of clinical case definitions for influenza can be low and can vary depending on the cocirculation of other respiratory pathogens.[23-26]

To address these issues, we studied the effectiveness and societal cost-benefit of vaccinating healthy working adults against influenza during the 1997-1998 and 1998-1999 influenza seasons.

METHODS

Study Design and Population

We conducted a double-blind, randomized, placebo-controlled trial of inactivated influenza vaccine among healthy working adults during the 1997-1998 and 1998-1999 influenza seasons. Persons eligible to participate were aged 18 to 64 years, were full-time employees of Ford Motor Co, Dearborn, Mich, did not have any medical conditions for which influenza vaccine was recommended by the US Advisory Committee on Immunization Practices, and did not have any contraindications to vaccination.[27] Participants were recruited through e-mail notices and study presentations at the work site. Written informed consent was obtained from all participants. The study was approved by the institutional review board at the Centers for Disease Control and Prevention (CDC), Atlanta, Ga.

Protocol

During enrollment in October of each study year, eligibility was determined, informed consent was obtained, and information on demographics, household composition and income, prior influenza vaccination, smoking, and health care costs was collected from participants by trained interviewers. Participants were given thermometers and instructed to record temperatures and symptoms during any respiratory illness episodes in a study log book as an aid to completing subsequent surveys. Participants were then randomly assigned, using a random-numbers table, to receive either trivalent inactivated influenza vaccine (FluShield, Wyeth-Lederle, Paoli, Pa) or sterile saline injection as a placebo. Participants in 1997-1998 were rerandomized if they participated in 1998-1999. Vaccine and saline were drawn up in identical syringes by 1 nurse and were administered by a different nurse who was blinded to participant randomization. Blinding was maintained until data collection was complete.

From November through March in each study year, participants were sent follow-up surveys by e-mail twice monthly that collected information on respiratory illnesses and related physician visits, medications, hospitalizations, and lost workdays. Responses were returned electronically and the data were entered directly into a secure database. Participants also were sent by e-mail a questionnaire regarding adverse effects that occurred in the first 7 days after receiving the injection. A questionnaire sent at the end of the study asked participants if they had received any influenza vaccine other than the study injection since enrollment and asked them to guess whether they received vaccine or placebo. Reminder e-mails were sent if completed surveys were not received after 1 week. Participants were telephoned a minimum of 2 times if electronic responses were not received by 1 week after the reminder e-mail was sent.

Virologic Surveillance and Serologic Studies

The influenza period was defined as the period during which clinical specimens collected from ill study participants yielded influenza viruses. During November through April of each study year, throat swabs, nasopharyngeal swabs, or both, were collected from participants who notified the study nurse of an influenzalike illness (ILI) and who had been ill for 4 days or less. Specimens were refrigerated at 4°C (39°F) until they were sent by overnight mail to either the Kaiser Permanente Laboratory (Los Angeles, Calif; 1997-1998) or the Michigan State Department of Health Laboratory (Lansing; 1998-1999), for viral culture. Influenza isolates from study participants were sent to the CDC and antigenically characterized.[28] Isolates were used only to characterize seasonal strains and were not used to define clinical illness.

Blood samples were collected prior to injection, 3 weeks after injection, and at the end of the season from approximately the first 300 participants enrolled each year. These samples were tested to provide laboratory-confirmed estimates of influenza infection rates. Not all participants could be tested because of resource limitations. In 1997-1998, a total of 298 persons provided preinjection blood samples and 275 (92%) returned for the end-of-season blood sample collection. In 1998-1999, a total of 278 (94%) of 296 persons had complete blood sample collection.

Serum was separated from blood and stored at –20°C until it was tested using hemagglutination inhibition (HI) at the CDC.[28] For 1997-1998, the HI test antigens were vaccine strains A/Johannesburg/82/96(H1N1), A/Nanchang/933/95(H3N2), and B/Harbin/7/94; reference outbreak strain A/Sydney/5/97(H3N2); and outbreak strain A/Michigan/8/98(H3N2). For 1998-1999, HI test antigens were vaccine strains A/Beijing/262/95(H1N1), A/Sydney/5/97(H3N2), and B/Harbin/7/94; and outbreak strain A/Michigan/15/99(H3N2). An HI antibody titer of less than 10 was assigned a value of 5. A 4-fold or greater rise in antibody titer against either a vaccine strain or an outbreak strain between the 3-week-postinjection and end-of-season serum samples was considered evidence of influenza infection.

Outcome Measures

The primary outcome measures were clinically defined respiratory illnesses and

associated physician visits and lost workdays during the influenza period.

Clinical respiratory illness was defined in 2 ways: (1) ILI was defined as feverishness or a measured temperature of at least 37.7°C (≥100°F) plus cough or sore throat (CDC ILI surveillance definition)[29]; and (2) upper respiratory illness (URI) was defined as sore throat plus cough, feverishness, or a measured temperature of at least 37.7°C (≥100°F).[6]

For the subset of patients from whom serum samples were collected, an influenza illness was defined as an ILI with laboratory evidence of influenza infection. Vaccine efficacy against laboratory-confirmed influenza illness was calculated as 1 minus the relative risk for laboratory-confirmed influenza illness among the vaccine group vs the placebo group. Vaccine effectiveness against clinically defined URI or ILI was similarly calculated.[26]

Economic Analysis

For both study years, we compared the costs associated with ILI in the placebo group with the costs and benefits associated with vaccination. The perspective taken was societal, and the economic cost of a clinical case of ILI was valued using the human capital approach.[30] This approach translates interventions and health outcomes into dollar amounts and includes the costs associated with work productivity. Thus, both direct costs (eg, physician visits, prescriptions, over-the-counter [OTC] medications, co-payments), and indirect costs (eg, time lost from work) are included, regardless of the payer.[30]

We also calculated the cost-benefit of vaccinating healthy working adults using a health care payer perspective (eg, an insurance company), which includes costs for physician visits, hospitalizations, prescriptions, and costs of the vaccine plus vaccine administration. Excluded from this perspective are costs borne by persons who become ill, such as for co-payments and OTC medications, as well as time lost from work.

For reasons of confidentiality, we were unable to obtain actual costs related to physician visits or salaries of each study participant. Therefore, we used the following methods: Physician visit diagnoses and prescription medication use were reported by participants, and the visits were assigned an *International Classification of Diseases, Ninth Revision* (*ICD-9*) code by investigators. A large health insurance database of persons aged 18 to 64 years in the Northeast Central region of the United States[31] was used to obtain the median insurance payments for *ICD-9*-coded visits and related prescriptions. The weighted average payment of all physician visits and associated prescriptions was calculated by weighting the median costs by the proportion of participants who reported each diagnosis. An 8-hour workday was valued at $29.39 per hour for wages plus benefits for professional specialty and technical civilians in goods-producing industries in large US companies in 1999.[32] The cost of vaccination was valued at $10 for the vaccine and its administration[6] (assuming a cost of $2.66 for the vaccine and supplies plus 15 minutes of a nurse's time, valued at $29.37 per hour for wages plus benefits[32]), and was added to 30 minutes of time lost from work[6] ($14.70 for wages plus benefits at $29.39 per hour[32]), for a total cost of $24.70 per person vaccinated.

Sensitivity Analysis

We conducted a sensitivity analysis in which labor costs, time lost from work for vaccination, and ILI attack rates were varied. In this analysis, only 1 variable was changed at a time from the values used in 1998-1999, which we considered the base case. Most of the study participants had a rate of hourly wages plus benefits that was notably greater than the US average.[32] Thus, we recalculated the results from our study using the US average rate of $20.29 per hour for an 8-hour workday for wages plus benefits.[32] We also examined the impact of different costs of vaccination by varying the amount of time lost from work for vaccination from 10 minutes to 60 minutes. In addition, we estimated societal costs when the ILI rates were varied from 0.5 to 2 times the rates observed in our study population in 1998-1999.

Statistical Analysis

A sample size of 1300 participants was calculated on the basis of an influenza attack rate of 5% among unvaccinated persons, vaccine efficacy of 60%, a confidence level of 95%, and 80% power. To assess the maintenance of blinding, actual injection assignments vs the assignments guessed by participants were compared using the κ statistic. Participants who answered "don't know" to the question about assignment were divided equally among the groups who guessed incorrectly and correctly. Differences between proportions were tested using the Fisher exact test.

An intention-to-treat analysis was performed, in which all persons who were randomized were included in the analysis, regardless of the completeness of their data. Outcomes data for persons with no completed surveys from the influenza period (n=7 in 1997-1998 and n=9 in 1998-1999) were imputed using baseline demographic characteristics. Differences between groups for continuous variables were tested using Poisson regression and adjusted for the number of completed surveys (PROC GENMOD, SAS, Version 6.12; SAS Institute Inc, Cary, NC). Analyses were performed including and excluding imputed cases.

RESULTS

Study Participants

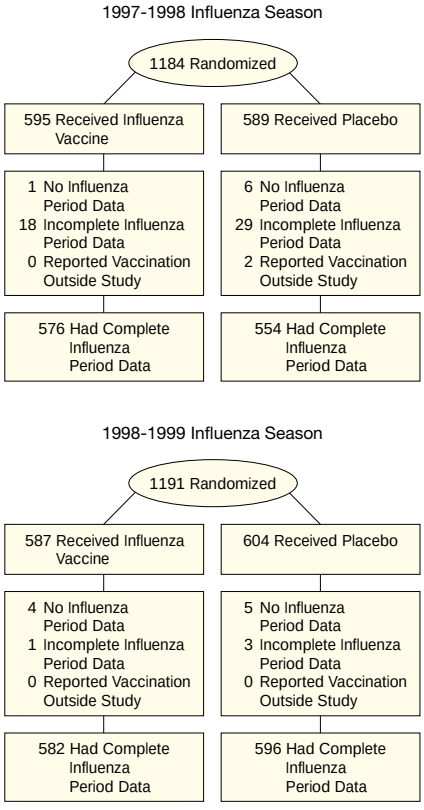
A total of 1184 participants were randomized in 1997-1998 and 1191 in 1998-1999 (FIGURE 1). Characteristics of randomized participants are shown in TABLE 1.

Virologic Surveillance

For 1997-1998, the influenza period was December 8, 1997, through March 2, 1998. During this period, 20 (23%) of 87 viral culture specimens collected from ill study participants were positive for influenza A. Isolates were characterized as

A/Sydney/5/97–like(H3N2) viruses, a strain that was antigenically distinct from the 1997–1998 H3N2 vaccine component.[33] For 1998-1999, the influenza period was January 4 through March 14, 1999, and 14 (23%) of 61 samples were culture-positive for influenza; 10 were influenza A(H3N2) and 4 were influenza B. The influenza A isolates were characterized as A/Sydney/5/97–like(H3N2) viruses and the B isolates were characterized as B/Beijing/184/93–like viruses, both of which were similar to the 1998-1999 influenza vaccine viruses.[34] These influenza periods were similar to those reported nationally.[33,34]

Figure. Study Participant Flow Diagrams



Data are shown for participant randomization and completeness of data for the 1997-1998 and 1998-1999 influenza season study years.

Adverse Effects and Blinding

During both study years, only arm soreness (for 1997-1998, 315 [53%] of 594 vs 106 [18%] of 586 [$P<.001$]; for 1998-1999, 309 [53%] of 582 vs 130 [22%] of 595 [$P<.001$]) and redness at the injection site (for 1997-1998, 86 [14%] of 594 vs 34 [6%] of 586 [$P<.001$]; for 1998-1999, 92 [16%] of 582 vs 45 [8%] of 595 [$P<.001$]) were reported more often by vaccine recipients than by placebo recipients. No other adverse effects, including fever, myalgia, headache, fatigue, rhinitis, or sore throat, were reported significantly more often by vaccine recipients, nor did they report significantly more lost workdays or physician visits.

In 1997-1998, 356 participants (30%) guessed their injection assignment correctly, 285 (24%) guessed incorrectly, 512 (43%) replied "don't know," and 31 (3%) did not reply ($\kappa=.062$) compared with 369 (31%), 290 (24%), 515 (43%), and 17 (1%), respectively, in 1998-1999 ($\kappa=.067$). In both years, 56% of participants who guessed identified their injection assignment correctly.

Influenza Illness Vaccine Efficacy

In 1997-1998, 3 (2.2%) of 138 vaccine recipients and 6 (4.4%) of 137 placebo recipients had laboratory-confirmed influenza illness (vaccine efficacy, 50%; $P=.33$). In 1998-1999, 2 (1%) of 141 vaccine recipients and 14 (10%) of 137 placebo recipients had influenza illness (vaccine efficacy, 86%; $P=.001$). Vaccine efficacy was 89% ($P=.001$) against influenza A/Sydney/5/97 and 60% ($P=.06$) against influenza B/Beijing/184/93.

Effectiveness Against Clinical Illness

During the 1997-1998 influenza season, vaccine recipients reported significantly more ILI-related sick days, lost workdays, and lost work hours for physician visits than placebo recipients (TABLE 2). Placebo recipients reported from 1 through 37 sick days (4 reported ≥25 sick days) and from 0 through 7 lost workdays per ILI, while vaccine recipients reported from 1 through 49 sick days

Table 1. Characteristics of Study Participants, 1997-1998 and 1998-1999

Characteristics	1997-1998 Vaccine Group (n = 595)	1997-1998 Placebo Group (n = 589)	1997-1998 *P* Value	1998-1999 Vaccine Group (n = 587)	1998-1999 Placebo Group (n = 604)	1998-1999 *P* Value
Age, median, y	44	43	.99	44	44	.99
Male, No. (%)	466 (78)	471 (80)	.52	452 (77)	453 (75)	.46
Nonsmokers, No. (%)*	547 (92)	530 (90)	.27	537 (91)	556 (92)	.75
Secondary smoke exposure in household, No. (%)†	60 (10)	37 (6)	.02	45 (8)	40 (7)	.50
Household size, median	3	3	.39	3	3	.60
No. (%) of households with children in						
Day care	81 (14)	92 (16)	.37	81 (14)	73 (12)	.40
Grades K-5	141 (24)	140 (24)	.99	136 (23)	136 (23)	.84
Grades 6-12	138 (23)	142 (24)	.73	126 (21)	149 (25)	.19
Vaccinated in year prior to study, No. (%)‡	78 (13)	65 (11)	.29	163 (28)	147 (24)	.19
Household income ≥$70 000/y, No. (%)§	430 (75)	427 (76)	.95	402 (75)	420 (78)	.35
Participated in study during 1997-1998, No. (%)‖	NA	NA		263 (45)	280 (46)	.60

*Did not smoke in past year or never smoked.
†For 1997-1998, n = 588 for placebo group.
‡For 1997-1998, n = 594 for vaccine group.
§For 1997-1998, n = 571 for vaccine group and n = 565 for placebo group. For 1998-1999, n = 533 for vaccine group and n = 539 for placebo group.
‖NA indicates data not applicable.

(14 reported >25 sick days) and from 0 through 24 lost workdays (1 vaccine recipient who was hospitalized with pneumonia reported 24 lost workdays). Vaccine effectiveness was –10% (P=.45) against ILI and –3% (P=.75) against URI during 1997-1998.

During 1998-1999, vaccine recipients reported 34% fewer ILIs, 42% fewer physician visits, and 32% fewer lost workdays (Table 2). Similar trends were seen for URIs, although the differences were statistically significant only for lost workdays (Table 2). Vaccine effectiveness was 33% (P=.003) against ILI and 13% (P=.23) against URI. Compared with the ILI definition, use of the URI definition resulted in inclusion of 40% more illnesses, 14% additional physician visits, and 6% more lost workdays. No study participants were hospitalized during 1998-1999. Combining data from both years and both study groups, the average ILI resulted in 0.38 physician visits and 0.79 days lost from work.

Economic Analysis

From the societal perspective, in 1997-1998, the net ILI cost per vaccinated person was $40.89 more than for un-

Table 2. Numbers and Rates per Person of Outcomes During 1997-1998 and 1998-1999*

	1997-1998						1998-1999					
	Vaccine Group (n = 576)		Placebo Group (n = 554)		% Difference in Rate, (Placebo – Vaccine)/ Placebo	P Value	Vaccine Group (n = 582)		Placebo Group (n = 596)		% Difference in Rate, (Placebo – Vaccine)/ Placebo	P Value
	Total Outcomes	Rate	Total Outcomes	Rate			Total Outcomes	Rate	Total Outcomes	Rate		
Influenzalike Illnesses												
Illnesses	161	0.280	132	0.238	−18	.25	82	0.141	128	0.215	34	<.001
Days ill	1374	2.385	957	1.727	−38	.01	592	1.017	920	1.544	34	<.001
Physician visits	64	0.111	48	0.087	−28	.19	29	0.050	51	0.086	42	<.001
Times any drug was prescribed	47	0.082	45	0.081	−1	.60	26	0.045	40	0.067	33	.005
Times antibiotic was prescribed	33	0.057	39	0.070	19	.09	24	0.041	33	0.055	25	.047
Times any over-the-counter drug was purchased	127	0.220	99	0.179	−23	.06	63	0.108	98	0.164	34	.001
Hospitalizations	1	0.002	0	0.000	NA	.50	0	0.000	0	0.000	NA	NA
Lost workdays	167	0.290	111	0.200	−45	.047	48	0.082	72	0.121	32	.002
Patients with any lost workdays	45	0.078	51	0.092	15	.15	45	0.077	69	0.116	34	<.001
Lost work hours for physician visits	99	0.172	20	0.036	−378	<.001	22	0.038	43	0.072	47	<.001
Patients with any lost work hours for physician visits	14	0.024	8	0.014	−71	.02	9	0.015	15	0.025	40	.004
Upper Respiratory Tract Illness												
Illnesses	259	0.450	232	0.419	−7	.57	137	0.235	156	0.262	10	.32
Days ill	2145	3.724	1775	3.204	−16	.14	988	1.698	1155	1.938	13	.21
Physician visits	84	0.146	62	0.112	−30	.14	41	0.070	50	0.084	17	.21
Times any drug was prescribed	62	0.108	54	0.097	−11	.75	33	0.057	39	0.065	12	.32
Times antibiotic was prescribed	46	0.080	48	0.087	8	.45	30	0.052	34	0.057	9	.49
Times any over-the-counter drug was purchased	200	0.347	170	0.307	−13	.21	103	0.177	118	0.198	11	.29
Hospitalizations	1	0.002	0	0.000	NA	.50	0	0.000	0	0.000	NA	NA
Lost workdays	177	0.307	117	0.211	−46	.02	56	0.096	71	0.119	19	.07
Patients with any lost workdays	55	0.096	57	0.103	7	.32	54	0.093	70	0.117	21	.047
Lost work hours for physician visits	109	0.189	28	0.051	−271	<.001	32	0.055	43	0.072	24	.10
Patients with any lost work hours for physician visits	18	0.031	10	0.018	−42	<.001	13	0.022	16	0.027	19	.26

*Inclusion of imputed data for persons without influenza period data did not affect results of statistical analyses. NA indicates data not applicable.

vaccinated persons (TABLE 3). When the cost of vaccination was included, the net societal cost difference increased to $65.59 per person. The main reason for the large difference is that the vaccine group had higher costs due to hospitalization ($13.53 per person vs $0 per person) and lost workdays ($68.28 per person vs $47.05 per person) than the placebo group. In 1998-1999, the net societal ILI cost per vaccine recipient was $13.53 less than the cost per placebo recipient (Table 3). However, when the cost of vaccination was included, vaccination resulted in a net societal loss of $11.17 per person (Table 3).

From the perspective of the health care payer, in 1997-1998, vaccination resulted in a net cost of $31.40 per person ($21.40 for physician visits, prescriptions, and hospitalizations plus $10 for vaccine and vaccine administration) vs a net cost of $6.99 per placebo recipient (Table 3). In 1998-1999, vaccination resulted in a net cost to the health care payer of $13.93 per vaccine recipient ($3.92 for physician visits, prescriptions, and hospitalizations plus $10 for vaccine and vaccine administration) vs a net cost of $6.27 per placebo recipient (Table 3). Thus, a health care payer would not have saved money as a result of vaccine administration in either year.

Sensitivity Analysis

When the estimated cost for a lost 8-hour workday was reduced from $235.10 (the base-case rate) to the 1999 US average of $162.32, or when the estimated time lost from work to receive

Table 3. Average Cost per Person for Influenzalike Illness (ILI) Among Vaccine and Placebo Groups by Study Year

Cost Categories	Cost per Category, $	Vaccine Group			Placebo Group		
		No. of Events/ No. of ILIs	No. of ILIs per Person*	Cost per Person, $†	No. of Events/ No. of ILIs	No. of ILIs per Person*	Cost per Person, $†
1997-1998‡							
Direct costs							
Physician visits§	34.39	64/161	0.280	3.83	48/132	0.238	2.98
Physician visit co-payments	10.00	64/161	0.280	1.11	48/132	0.238	.87
Prescriptions§‖	49.38	47/161	0.280	4.04	45/132	0.238	4.01
Prescription co-payments	12.40	47/161	0.280	1.01	45/132	0.238	1.01
Cost of over-the-counter drugs, $¶		1527/161	0.280	2.66	912/132	0.238	1.64
Hospitalizations§	7790.70	1/161	0.280	13.53	0	0.238	0.00
Indirect costs							
Lost workdays#	235.10	167/161	0.280	68.28	111/132	0.238	47.05
Lost work hours for physician visits	29.39	99/161	0.280	5.06	20/132	0.238	1.06
Average ILI cost per person				**99.51**			**58.62**
Cost of vaccination**				24.70			0.00
Vaccination and ILI cost per person				**124.21**			**58.62**
1998-1999							
Direct costs							
Physician visits§	34.39	29/82	0.141	1.71	51/128	0.215	2.95
Physician visit co-payments	10.00	29/82	0.141	.50	51/128	0.215	.86
Prescriptions§‖	49.38	26/82	0.141	2.21	40/128	0.215	3.32
Prescription co-payments	12.40	26/82	0.141	.55	40/128	0.215	.83
Cost of over-the-counter drugs, $¶		728/82	0.141	1.25	1043/128	0.215	1.75
Hospitalizations§	7790.70	0	0.141	0.00	0	0.215	0.00
Indirect costs							
Lost workdays#	235.10	48/82	0.141	19.40	72/128	0.215	28.43
Lost work hours for physician visits	29.39	22/82	0.141	1.11	43/128	0.215	2.12
Average ILI cost per person				**26.73**			**40.26**
Cost of vaccination**				24.70			0.00
Vaccination and ILI cost per person				**51.43**			**40.26**

*Rates are from Table 2.
†Cost per person was calculated by multiplying the cost per category by the number of events per ILI by the number of ILIs per person.
‡In 1997-1998, only the number of total days ill, lost workdays, and lost work hours for physician visits were significantly different between the vaccine and placebo groups (see Table 2).
§Median costs for physician visits, prescription medications, and hospitalizations in 1996 were obtained from the MarketScan database and adjusted to 1999 dollars (Table 5).[31] Study participants reported a median co-payment of $10 per physician visit.
‖The average number of prescriptions per physician visit, weighted by *International Classification of Disease, Ninth Revision*–coded visits and based on MarketScan data (Table 5),[31] was 2.48 prescriptions per visit. Study participants reported a median co-payment of $5 per prescription.
¶Participants reported the number of dollars spent on over-the-counter drugs.
#The estimated average cost for a lost workday was based on the hourly rate for wages plus benefits for civilian workers in goods-producing industries in large US companies in 1999 and is based on an 8-hour workday at $29.39/h.[32]
**The cost of vaccination was estimated as the cost of the vaccine and vaccine administration ($10) plus the cost of time lost from work for vaccination. In this case, 30 minutes (resulting in a cost of $14.70) was the estimated time that a person would miss work to receive a vaccine. Thus, the total cost of vaccination was estimated to be $24.70.

the vaccination was varied from 10 to 60 minutes from the base-case time of 30 minutes, the societal cost of vaccination remained higher than the cost of no vaccination (TABLE 4). When the base-case ILI rates were reduced by 50% among both vaccine and placebo groups, the net societal loss increased to $17.94 per person. However, doubling the base-case rates of ILI resulted in a net societal benefit of $2.36 per person vaccinated (Table 4).

COMMENT

Influenza vaccination can have substantial health benefits for persons of any age. Studies have repeatedly demonstrated that influenza vaccination of persons aged 65 years or older is also economically beneficial.[1-4,35] It is less certain whether vaccinating healthy working adults younger than 65 years against influenza would result in societal cost savings.

A study of healthy working adults in Minnesota during the 1994-1995 influenza season found a net societal benefit of $46.85 per person vaccinated and a 35% reduction in URI.[6] Influenza infection rates and vaccine efficacy estimates were not available in that study because confirmatory diagnostic laboratory tests were not conducted. However, other studies of healthy adults have not found similar results, and reviews have concluded that influenza vaccination of healthy adults is unlikely to result in a net cost savings to society.[5,12]

Our randomized, placebo-controlled study was conducted to further evaluate the health and economic benefits of vaccinating healthy adults. This study was notable because it was conducted during 2 consecutive influenza seasons, it defined the influenza period based on virologic surveillance at the study site, and it used diagnostic testing to confirm influenza infection rates in a subset of participants. This study also used e-mail as the primary means for data collection, which might have contributed to the high participation rate.

Vaccination of healthy working adults provided no overall economic benefit in either year of our study. Furthermore, we were not able to replicate the economic or clinical illness results found in the Minnesota study, even when we used a similar URI case definition (ie, sore throat and either fever or cough).[6] In particular, it should be noted that the URI rate among placebo recipients in the Minnesota study was 3.3 to 5.3 times higher than among placebo recipients in our study. In our sensitivity analysis, we found that doubling the ILI rate did result in a net cost savings to society of $2.36 per person. However, doubling the ILI rate would presumably also increase the laboratory-confirmed illness rate among the placebo group from 10% to 20%. During nonpandemic influenza years, influenza illness rates among adults younger than 65 years are generally less than 10%, and influenza illness rates of 20% or greater would be expected to occur very infrequently.[14,16-18]

In addition to having substantially different illness rates, other factors in our study also may have contributed to results that are different from those reported in the Minnesota study. The 2 study populations differed by age, sex, income level, and other variables.[6] It is also possible that a lower proportion of the total respiratory illnesses in our study were caused by influenza, thereby reducing our estimate of vaccine effectiveness.[26] This point underscores the importance of using laboratory tests to confirm a subset of clinically defined cases in such studies. Studies of case definitions of influenza have shown that requiring presence of fever in a clinical case definition substantially increases the specificity of the clinical diagnosis.[23-25] Since the URI case definition is relatively broad and does not require presence of fever, its use to estimate vaccine effectiveness can be expected to dilute the observable benefit of the vaccine.[26]

We were not able to completely maintain blinding with regard to vaccine status in our study, similar to other studies of inactivated influenza vaccine that used saline as a placebo.[6,10,19] This is not surprising because arm soreness and redness at the injection site are associated

Table 4. Effects of Varying Costs of Lost Workdays and Vaccination and Rates of Influenzalike Illness (ILI) on Difference in Cost of ILI Between Vaccine and Placebo Groups, 1998-1999

Cost Variables	Vaccination Cost, $	ILI Cost per Vaccine Recipient, $	ILI and Vaccine Cost per Vaccine Recipient, $	ILI Cost per Placebo Recipient, $	Societal Cost Difference (Placebo–Vaccine), $
1998-1999*	24.70	26.73	51.43	40.26	−11.17
US average wages, 8-hour workday†	20.15	20.39	40.54	30.81	−9.73
Time lost from work for vaccination‡					
10 min	14.90	26.73	41.63	40.21	−1.37
60 min	39.39	26.73	66.12	40.21	−25.86
ILI rate§					
0.5 times base-case rate	24.70	13.37	38.07	20.13	−17.94
2 times base-case rate	24.70	53.46	78.16	80.52	2.36

*See Tables 2 and 3. The cost of vaccination was calculated by adding the cost of the vaccine and vaccine administration ($10) and 30 minutes lost from work for vaccination. An 8-hour workday was valued at $29.39/h for wages plus benefits in 1999 dollars.
†An 8-hour workday was valued at $20.29/h for wages plus benefits in 1999 dollars.
‡The cost of vaccination was altered by decreasing or increasing the amount of time lost from work from the 30 minutes initially assumed.
§The rates of ILI per person among vaccine and placebo groups during 1998-1999 (see Tables 2 and 3) were varied from 0.5 times to 2 times the 1998-1999 ILI rate. Thus, the rate of ILI in the vaccine group was varied from 0.141 ILIs per person to 0.0705 ILIs per person and 0.282 ILIs per person. For the placebo group, the rate of 0.215 ILIs per person was varied from 0.1075 ILIs per person to 0.430 ILIs per person.

with vaccination against influenza and participants were informed about potential adverse effects as part of the consent process. Although the extent to which this could have biased our findings is unknown, the illness rates and related costs found in our study were comparable with those seen in studies using similar case definitions.[11,18,23,35]

In 1998-1999, when the vaccine and circulating influenza strains were well matched, vaccination clearly had health benefits. In that year, the vaccine efficacy against laboratory-confirmed influenza was 86% and there were statistically significant reductions in ILI, physician visits, and days lost from work among vaccine recipients. In the first year of the study, 1997-1998, when the vaccine and circulating strains were not well matched, the difference between the rates of ILI in the vaccine and placebo groups was not statistically significant.

In interpreting the results of our study, several important points should be kept in mind. First, rates of influenza-associated severe illness and hospitalization, and subsequent cost per illness, are generally much lower in healthy young adults than in elderly persons.[5,36] Second, the rates of laboratory-confirmed influenza illness in this study (1%-10%) were similar to those found in other studies of adults. In those studies, influenza infection rates ranged from 1% to 26% per year, but approximately two thirds of the years had rates less than 10%.[14,16-18] In our study, as in most studies, only a minority of the respiratory illnesses among adults were due to influenza.[25,37-39] Third, in approximately 1 of every 10 years, there is a poor antigenic match between vaccine strains and the predominant circulating influenza viruses (Nancy J. Cox, PhD, unpublished data, August 2000).

The cost estimates applied to this study population (TABLE 5) may not be generalizable to other populations, particularly those with lower incomes or those that lack health care access.[21] However, use of lower labor cost estimates would be expected to further diminish the likelihood of finding cost savings from vaccination. The vaccination cost estimated in our study did not include additional costs for adverse events from vaccination since no additional labor or medical costs were reported in our study. Influenza vaccine–associated adverse events that require medical attention are uncommon and the reported adverse effects and adverse events in our study are similar to those in other studies of healthy adults.[6,10,18,27] In our economic analysis, we also did not consider the potential benefits of reducing transmission of influenza to coworkers and household members or the potential benefit of intangibles, such as avoiding the discomforts and inconveniences associated with influenza illness. Including these factors could have increased the likelihood of finding cost

Table 5. Outpatient Physician Visit Costs and Prescription Costs, by *ICD-9* Code*

			Physician Visits		Prescriptions		
ICD-9 Code	Diagnosis	No. (%) of Patients Reporting Diagnosis	Median Cost, 1996 $†	Weighted Average Cost per Patient in Study, 1999 $‡	Median Cost, 1996 $§	Average No. of Prescriptions per Patient§	Weighted Average Cost per Patient in Study, 1999 $‖
034.0	Strep throat	14 (6.8)	9.38	0.70	12.81	2.2	2.09
382.9	Otitis media, not otherwise specified	4 (2.0)	33.25	0.72	17.84	2.6	1.01
460	Acute nasopharyngitis (upper respiratory tract infection)	56 (27.3)	33.00	9.82	15.40	2.0	9.16
461.9	Acute sinusitis, not otherwise specified	38 (18.5)	34.50	6.96	20.00	3.0	12.10
462	Acute pharyngitis	6 (2.9)	30.50	0.96	13.71	2.3	1.00
463	Acute tonsillitis	3 (1.5)	31.38	0.51	10.67	1.9	0.33
466.0	Acute bronchitis	27 (13.2)	35.50	5.11	28.55	2.9	11.91
486	Pneumonia, organism unspecified	5 (2.4)	31.63	0.83	20.25	2.8	1.48
487.1	Influenza, not otherwise specified	52 (25.4)	31.75	8.79	14.88	2.5	10.30
Total		**205 (100)**		**34.39**			**49.38**

**ICD-9* indicates *International Classification of Diseases, Ninth Revision*. Median costs were obtained from the MarketScan database[31] for 1996. These data relate to patients in the database who are employed in the Northeast Central region of the United States who receive health insurance benefits from an employer in manufacturing (durable goods) industries.

†A total of 22 144 physician visits relating to the listed diagnoses were identified in the MarketScan database,[31] and the sample sizes for each *ICD-9* code were as follows: for 034.0, 753 visits; 382.9, 1626; 460, 207; 461.9, 3892; 462, 4861; 463, 488; 466.0, 5758; 486, 3629; and 487.1, 930.

‡A weighted cost per *ICD-9* code was calculated as follows: median cost per visit × inflation factor of 1.08971 (1996 to 1999, medical component of consumer price index) × weight of patients in study (percentage of patients in study with given diagnoses). The final weighted average is the sum of the individual weighted averages for each *ICD-9* code.

§A total of 32 078 prescriptions related to the listed diagnoses were identified in the MarketScan database,[31] and the sample sizes for each *ICD-9* code were as follows: for 0.34.0, 870 prescriptions; 382.9, 2285; 460, 207; 461.9, 6650; 462, 5788; 463, 426; 466.0, 9735; 486, 4880; 487.1, 1237. The average number of prescriptions per *ICD-9* code were obtained from the MarketScan database.[31]

‖A weighted cost per *ICD-9* code was calculated as follows: median cost per prescription × average prescriptions per patient × inflation factor of 1.08971 (1996 to 1999, medical component of consumer price index) × weight of patients in study (percentage of patients in study with given diagnoses). The final weighted average is the sum of the individual weighted averages for each *ICD-9* code.

savings. Regardless of the cost-benefit of influenza vaccination in healthy adults, some working adults may choose to be vaccinated to reduce their risk of being infected with influenza. However, results of this study could be used to help set societal priorities when vaccine is in short supply.

In conclusion, influenza infection is associated with substantial work absenteeism and health care resource use among healthy working adults. In years in which there is a good match between vaccine and circulating viruses, vaccination against influenza can have substantial health benefits by reducing rates of ILI, physician visits, and work absenteeism. Nonetheless, our results suggest that vaccination of healthy adults younger than 65 years is unlikely to provide societal economic benefit in most years.

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