Effectiveness of Live, Attenuated Intranasal Influenza Virus Vaccine in Healthy, Working Adults

A Randomized Controlled Trial

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Context Influenza virus is a major cause of illness, disruption to daily life, and increased use of health care in all age groups.

Objective To assess the safety and effectiveness of intranasally administered trivalent, live, attenuated influenza virus (LAIV) vaccine for reducing illness, absenteeism, and health care use among healthy, working adults.

Design Randomized, double-blind, placebo-controlled trial conducted from September 1997 through March 1998.

Setting Thirteen centers across the United States.

Participants A total of 4561 healthy, working adults aged 18 to 64 years recruited through health insurance plans, at work sites, and from the general population.

Intervention Participants were randomized 2:1 to receive intranasally administered trivalent LAIV vaccine (n = 3041) or placebo (n = 1520) in the fall of 1997.

Main Outcome Measures Episodes of febrile illness, severe febrile illness, febrile upper respiratory tract illness, work loss, and health care use during the peak and total influenza outbreak periods, and adverse events.

Results Recipients of LAIV vaccine were as likely to experience 1 or more febrile illnesses as placebo recipients during peak outbreak periods (13.2% for vaccine vs 14.6% for placebo; $P = .19$). However, vaccination significantly reduced the numbers of severe febrile illnesses (18.8% reduction; 95% confidence interval [CI], 7.4%-28.8%) and febrile upper respiratory tract illnesses (23.6% reduction; 95% CI, 12.7%-33.2%). Vaccination also led to fewer days of illness across all illness syndromes (22.9% reduction for febrile illnesses; 27.3% reduction for severe febrile illnesses), fewer days of work lost (17.9% reduction for severe febrile illnesses; 28.4% reduction for febrile upper respiratory tract illnesses), and fewer days with health care provider visits (24.8% reduction for severe febrile illnesses; 40.9% reduction for febrile upper respiratory tract illnesses). Use of prescription antibiotics and over-the-counter medications was also reduced across all illness syndromes. Vaccine recipients were more likely to experience runny nose or sore throat during the first 7 days after vaccination, but serious adverse events between the groups were not significantly different. The match between the type A(H3N2) vaccine strain and the predominant circulating virus strain (A/Sydney/05/97[H3N2]) for the 1997-1998 season was poor, suggesting that LAIV provided substantial cross-protection against this variant influenza A virus strain.

Conclusion Intranasal trivalent LAIV vaccine was safe and effective in healthy, working adults in a year in which a drifted influenza A virus predominated.

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Influenza type A and B viruses cause illness in 10% to 20% of the population each year.[1] Prominent manifestations of illness include decreased ability to perform daily activities and increased health care resource use. Among working adults, influenza accounts for millions of work-loss days and physician office visits each year.[2,3] Although healthy, working adults are not currently targeted for routine annual vaccination,[4] immunization with inactivated influenza virus vaccines can be associated with substantial health and economic benefits for this group.[5]

Live, attenuated influenza virus (LAIV) vaccines offer a new option for the prevention and control of influenza. These vaccines do not require an injection for administration and because intranasal administration results in infection with the attenuated virus strains, they may more effectively stimulate mucosal and cell-mediated immune responses.[1,6-9] Among children, monovalent and bivalent vaccines are at least as efficacious as inac-

For editorial comment see p 182.

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tivated influenza virus vaccines.[10,11] In a recent placebo-controlled trial among children aged 15 to 71 months, intranasally administered trivalent LAIV vaccine reduced culture-confirmed influenza infection by 93%.[12] Studies using primarily monovalent or bivalent formulations have shown that these vaccines are safe, immunogenic, and efficacious among healthy adults as well.[1,6,13-16] Trivalent LAIV vaccine has reduced experimentally induced influenza in adult volunteers by 85%.[17] A 5-year study of bivalent LAIV vaccine demonstrated protection against natural influenza A infection among children and adults that was approximately equivalent to that of trivalent inactivated vaccine.[18] The present study assesses the safety and effectiveness of trivalent LAIV vaccine among healthy adults for reducing clinical illness, absenteeism, and health care use.

METHODS

Design and Subjects

This study was a randomized, double-blind, placebo-controlled trial. Participants were enrolled from 13 sites across the continental United States between mid-September and mid-November 1997. Recruitment strategies differed by site and included recruitment through specific health insurance carriers and work sites as well as from the general population, using a variety of advertising media. Persons were eligible if they were 18 to 64 years old, they worked at least 30 h/wk outside of the home, they had health insurance, and they were available for follow-up telephone calls. Exclusion criteria included a history of acute hypersensitivity to eggs or egg products, previous receipt of the 1997-1998 inactivated influenza vaccine, self-reported pregnancy or unprotected risk for pregnancy within the previous 3 months, and acute febrile illness or upper respiratory tract illness within 72 hours. Because of the placebo-control arm of the study, exclusion criteria also included the presence of any indications for routine vaccination with the inactivated vaccine, such as the presence of high-risk medical conditions or positions of employment that involve significant contact with high-risk people. Study participants received up to $100 as a financial incentive. The study was approved by the institutional review board at each site and written informed consent was obtained from all participants.

Vaccine

The LAIV vaccine for the 1997-1998 season (FluMist, Aviron) included 3 live, attenuated influenza virus strains: A/Shenzhen/227/95 (H1N1), A/Wuhan/359/95 (H3N2), and B/Harbin/7/94-like, in egg allantoic fluid containing sucrose-phosphate-glutamate (SPG). These strains were antigenically equivalent to those included in the inactivated vaccine for the 1997-1998 season.[19] The placebo, which consisted of egg allantoic fluid containing SPG, was indistinguishable in appearance and smell from the vaccine. Vaccine and placebo were supplied in single-dose intranasal sprayers. Participants were provided with instructions on intranasal administration of the vaccine and were given the option of self-administration under direct supervision of or administration by a study staff member. To allow sufficient time for an immune response to develop before any anticipated influenza outbreaks, vaccine or placebo was administered between September 18 and November 15, 1997.

Randomization and Masking

Participants were randomized 2:1 to receive the investigational LAIV vaccine or placebo. To ensure balanced allocation of subjects between vaccine and placebo within each site, randomization was performed using 6-unit blocks. Participants were randomized at the time of vaccination. Each new participant was assigned to the next available sequential allocation number according to the predetermined, computer-generated randomization schedule. The sequential number imprinted on the vaccine label determined the material used for vaccination. Adherence to the predetermined allocation sequence was documented through accountability logs. Both the vaccine and placebo were prelabeled according to the computer-generated randomization schedule provided by Statistics Collaborative, Washington, DC, packaged to be visually identical, and delivered to the study sites by Almedica Service Corp, Waldwich, NJ. Blinding to intervention assignment of the study participants and site personnel was maintained until all outcome data had been collected and verified.

Data Collection

Baseline Data and Safety and Tolerability of Vaccine. Information on participant demographic characteristics, medical history, and current use of medications was collected at the time of enrollment. For assessment of post-vaccination reactogenicity symptoms and other adverse events, participants were given a reactogenicity symptom card and a digital thermometer and were instructed to record daily temperatures and check off the presence of respiratory tract symptoms (cough, sore throat, and runny nose) and other systemic symptoms (headache, chills, muscle aches, and tiredness or weakness) on a daily symptom checklist beginning on the evening of vaccination and daily thereafter for 7 days. They were also asked to list other symptoms and any medications used during the week following vaccination. Study personnel telephoned participants 7 days after vaccination to remind them to return the reactogenicity cards. Participants were also called 28 days after vaccination to identify the occurrence of any serious adverse events during the 28 days following vaccination that had not been reported on the reactogenicity cards. Assessment and recording of any additionally reported serious adverse events continued through the end of the study.

Illness Episodes, Health Care Use, and Work Loss. To assess occurrences of illness, health care use, and work loss for each month from November 1997 through March 1998, participants completed symptom and illness cards on which they daily checked off

symptoms present, including self-reported fever, respiratory tract symptoms (cough, sore throat, and runny nose) and other systemic symptoms (headache, chills, muscle aches, and tiredness or weakness). They also recorded whether they missed work, visited a health care provider, took antibiotics, and used over-the-counter medications for illness symptoms. A computer-generated telephone messaging system reminded participants to complete and return the cards.[20]

Regional Influenza Surveillance. For each recruitment site, a laboratory was identified that conducts influenza viral surveillance in the geographic area from which participants were recruited. These laboratories were contacted weekly from November 1997 through March 1998 for reports on the number of specimens submitted for influenza testing, the number of specimens with positive results, and strain identification, if performed. This information was supplemented by surveillance data from the Centers for Disease Control and Prevention, Atlanta, Ga. The combined data were used to define 2 influenza outbreak periods: site-specific peak outbreak periods and total outbreak periods. *Site-specific peak outbreak periods* were defined using a prespecified algorithm that began with the modal week for positive influenza isolates in the community around each study site and sequentially included weeks both before and after the peak week for which there were positive isolates until at least 80% of isolates for the season were included. The *total outbreak period* was defined by an expert panel blinded to study outcomes after inspection of histograms showing the numbers of positive isolates by week for all sites combined. During site-specific peak outbreak periods, it was expected that the clinically defined illness syndromes would have a greater degree of specificity for true influenza illness and would therefore provide a more precise estimate of vaccine effectiveness. The total outbreak period, on the other hand, was expected to provide a broader overall assessment of the impact of influenza and its prevention on the study population.

Illness Definitions

The primary effectiveness end point for the study was the proportion of participants reporting 1 or more *febrile illnesses* during the peak outbreak periods. Subjects were characterized as having a febrile illness if they had symptoms for at least 2 consecutive days, with fever on at least 1 day, and if they had 2 or more symptoms (fever, chills, headache, runny nose, sore throat, cough, muscle aches, tiredness/weakness) on at least 1 day. This illness category was expected to be quite sensitive but not very specific for true influenza illness. Two additional prespecified febrile illness syndromes that were expected to correlate with more severe illness and/or to have a higher degree of specificity for true influenza illness were examined. These included *severe febrile illness* (at least 3 consecutive days of symptoms, at least 1 day of fever, and 2 or more symptoms on at least 3 days) and *febrile upper respiratory tract illness* (at least 2 consecutive days of upper respiratory tract symptoms [runny nose, sore throat, or cough], fever on at least 1 day, and 2 symptoms on at least 1 day).

Analysis

All randomized participants were included in the analyses if they provided any safety and tolerability or clinical effectiveness data. Participants for whom no follow-up data were available were excluded from the analyses. Bivariate comparisons for the proportions of subjects experiencing study outcomes were conducted using the Cochran-Mantel-Haenszel test, controlling for site. Because the end points that measured counts such as the numbers of illness episodes were distributed approximately according to the Poisson distribution, we used generalized linear models to calculate the variance of the event rates to allow for hypothesis testing (PROC GENMOD, SAS, Version 6.12, SAS Institute Inc, Cary, NC). Outcome rates were adjusted for the duration of follow-up data available for each subject and the duration of the site-specific peak outbreak periods, when appropriate. For assessing the rates of adverse effects during the 7 days following vaccination, clinical equivalence was defined as occurring if the upper limit of a 2-sided 95% confidence interval (CI) for the difference in rates was no more than 5% for fever and no more than 10% for the other reactogenicity symptoms.

The sample size estimates for the trial were based on achieving 90% power for the primary effectiveness end point. At least 4200 participants would be required to have 90% power to detect a difference of 2.52%, assuming that 6% of placebo recipients would experience a febrile illness, 70% of these illnesses would be due to influenza, vaccine efficacy would be 60%, 3.48% of vaccine recipients would experience febrile illness, and outcome data would be available for 80% of participants. This sample size also afforded 99% power to demonstrate similar reactogenicity rates between vaccine and placebo recipients using the equivalence definitions provided herein.

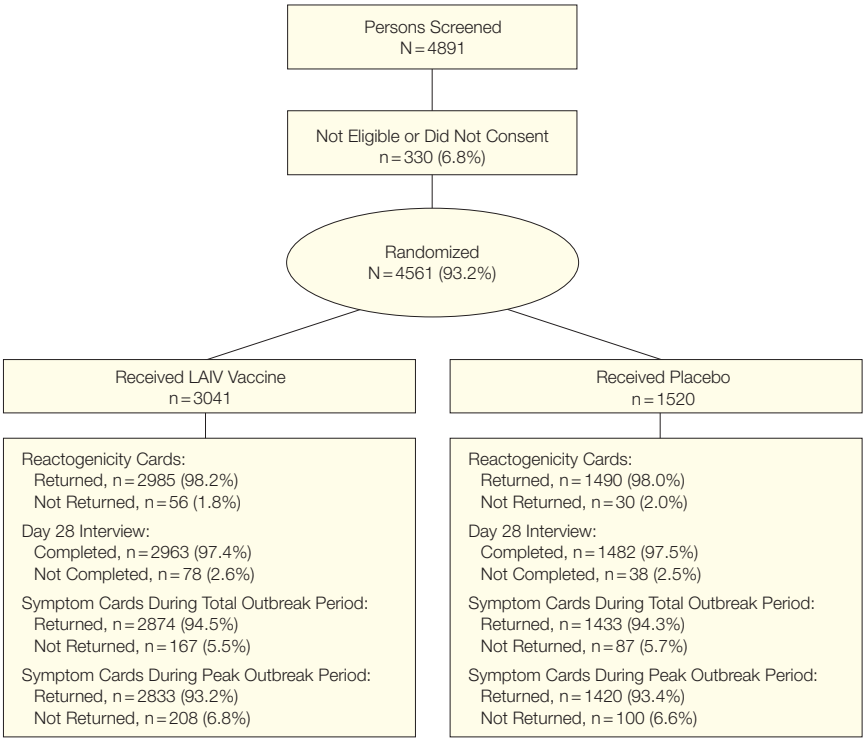
RESULTS

A total of 4561 persons were randomized from September 18 through November 15, 1997 (FIGURE 1). The demographic characteristics of the 3041 vaccine recipients and 1520 placebo recipients were well balanced between the groups (TABLE 1).

Adverse Effects

Seventy-one percent of vaccine recipients and 69% of placebo recipients self administered the vaccine or placebo. In both groups, 96% of persons self administering did so without difficulty. Reactogenicity data for the 7 days following vaccination were available for 98.2% of vaccine recipients and 98.0% of placebo recipients. Vaccine recipients were more likely than placebo recipients to experience a runny nose (44.3% vs 26.6%; difference, 17.7%; 95% CI for difference, 14.7%-20.7%) during the week following vaccination. Among persons with a runny nose, the duration was similar between the groups (median duration, 2 days for

Figure 1. Trial Profile



During the days 0-28 safety phase of the trial, 3 participants (2 in vaccine group [0.07%] and 1 in placebo group [0.07%]) withdrew because of adverse events. The 2 events among vaccine recipients were a hospitalization for Crohn disease and an accidental drowning complicated by acute alcohol intoxication. The event in a placebo recipient was related to psychiatric illness not requiring hospitalization. None of these events was judged to be related to receipt of the study treatment by the blinded study investigators. An additional 15 participants (10 in vaccine group [0.3%] and 5 in placebo group [0.3%]) either withdrew voluntarily or were noncompliant. Sixty-nine vaccine recipients (2.3%) and 31 placebo recipients (2.0%) were lost to follow-up and 2 others (1 in each group) cited other reasons for not providing the day 28 safety data. During the clinical effectiveness phase of the trial, participants who did not return the symptom cards were considered lost to follow-up. LAIV indicates live attenuated influenza virus.

Table 1. Characteristics of Study Participants*

	Vaccine Group (n = 3041)	Placebo Group (n = 1520)
Age, mean (SD) [range], y	38.3 (10.2) [18-65]†	38.2 (10.0) [18-65]†
Sex, female	1664 (54.7)	825 (54.3)
Race/ethnicity		
White	2576 (84.7)	1269 (83.5)
Black	292 (9.6)	166 (10.9)
Asian	69 (2.3)	38 (2.5)
Hispanic	68 (2.2)	32 (2.1)
Native American	10 (0.3)	3 (0.2)
Other	26 (0.8)	12 (0.8)
Highest level of education		
Up to 12th grade, no diploma	60 (2.0)	30 (2.0)
High school graduate	509 (16.7)	297 (19.5)
Some college or associate's degree	1008 (33.2)	496 (32.6)
Bachelor's degree	944 (31.0)	435 (28.6)
Advanced degree (master's, doctorate, professional)	520 (17.1)	261 (17.2)
Other	0 (0)	1 (0.7)

*$P \geq .13$ for all data comparisons. Data are presented as number (percentage) unless otherwise noted.
†Three subjects were 64 years old at enrollment but were 65 years when the study began.

both groups; 25th percentile, 1 day for both groups; 75th percentile, 4 days for vaccine group and 5 days for placebo group). Vaccine recipients were also more likely to report a sore throat (26.6% vs 16.3%; difference, 10.3%; 95% CI for difference, 7.7%-12.9%) during the week following vaccination. As with runny nose, the duration of sore throat symptoms was similar between the 2 groups (median duration, 2 days for both groups; 25th percentile, 1 day for both groups; 75th percentile, 3 days for both groups). Neither symptom resulted in increased use of antibiotics, analgesics/antipyretics, or decongestants/antihistamines/antitussives among vaccine recipients. The 2 groups had equivalent rates of other symptoms during the 7 days following vaccination (FIGURE 2).

During the 28 days following vaccination, 9 serious adverse events were reported: 5 among vaccine recipients (0.18%) and 4 among placebo recipients (0.27%; $P = .50$). These included 8 hospitalizations (4 in each group) and 1 death (vaccine group) due to an accidental drowning complicated by alcohol intoxication. None was judged by blinded study investigators to be related to the study treatment. An additional 49 serious adverse events were reported during the clinical effectiveness outcome periods, including 30 (1.0%) among vaccine recipients and 19 (1.3%; $P = .50$) among placebo recipients. Each represented a hospitalization judged by the blinded investigators not to be related to receipt of the study treatment.

Outbreak Isolates

The peak outbreak periods lasted from 4 to 12 weeks at the different sites, with a median duration of 7 weeks. The total outbreak period for all study sites combined extended from December 14, 1997, through March 21, 1998. This 14-week period was similar to that seen nationally for the 1997-1998 influenza season (FIGURE 3). More than 99% of influenza isolates from the study site laboratories were type A, and more than 99% of the subtyped isolates were

A(H3N2) viruses. This predominance was also similar to what was seen throughout the United States for that season.[21,22] Nationally, 80% of the further subtyped A(H3N2) viruses were A/Sydney/5/97-like, a drifted variant from the A(H3N2) component included in the vaccine.[21,22]

Outcomes

Vaccine recipients returned 10 869 (89.4%) of 12 164 symptom cards for the 4-month, 14-week pooled outcome period, while placebo recipients returned 5451 (89.7%) of 6080 cards. During the 14-week total outbreak period, 94.4% of participants returned at least 1 card, while 93.2% returned at least 1 card during the peak outbreak period. Fewer vaccine recipients (373/2833) experienced 1 or more febrile illnesses than did placebo recipients (207/1420) during the peak outbreak period, although this difference did not reach statistical significance (13.2% vs 14.6%; $P = .19$). Among vaccine recipients, 285 (73%) of all febrile illnesses were severe febrile illnesses and 240 (61%) were febrile upper respiratory tract illnesses. For placebo recipients, 173 (81%) of febrile illnesses were severe and 154 (72%) were febrile upper respiratory tract illnesses.

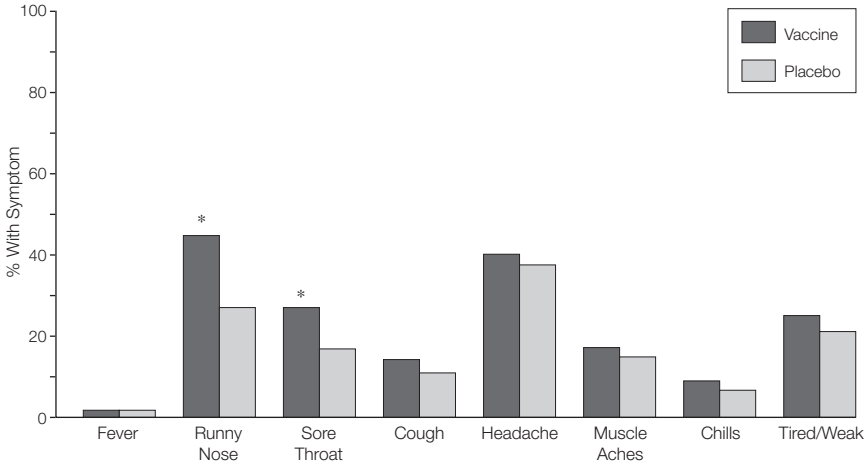
During the peak outbreak periods, vaccination reduced all outcomes in each prespecified illness category (TABLE 2). We observed a 10.0% to 23.6% reduction in the rates of illnesses ($P = .10$ for febrile illnesses; $P \leq .002$ for all others), a 22.9% to 27.3% reduction in total rates of days ill ($P < .001$ for all), a 13.1% to 28.4% reduction in work-loss days, ($P = .07$ for febrile illnesses; $P \leq .01$ for all others), and a 14.7% to 40.9% reduction in days with at least 1 health care provider visit ($P = .06$ for febrile illnesses; $P < .001$ for all others). Vaccination also led to reductions of 42.9% to 47.0% in the numbers of days subjects took prescription antibiotics ($P < .001$) and reductions of 23.3% to 28.0% in the numbers of days subjects took over-the-counter medications ($P < .001$) Findings for the total outbreak period were similar (TABLE 3).

COMMENT

In this study, intranasal trivalent LAIV vaccine was safe and well tolerated. Although it did not significantly reduce the proportion of persons experiencing at least 1 febrile illness, LAIV vaccine did significantly reduce the numbers of severe febrile illnesses and febrile upper respiratory tract illnesses among healthy, working adults. It also led to fewer numbers of days ill and lower rates of work absenteeism, health care provider visits, and use of prescription antibiotics and nonprescription medications.

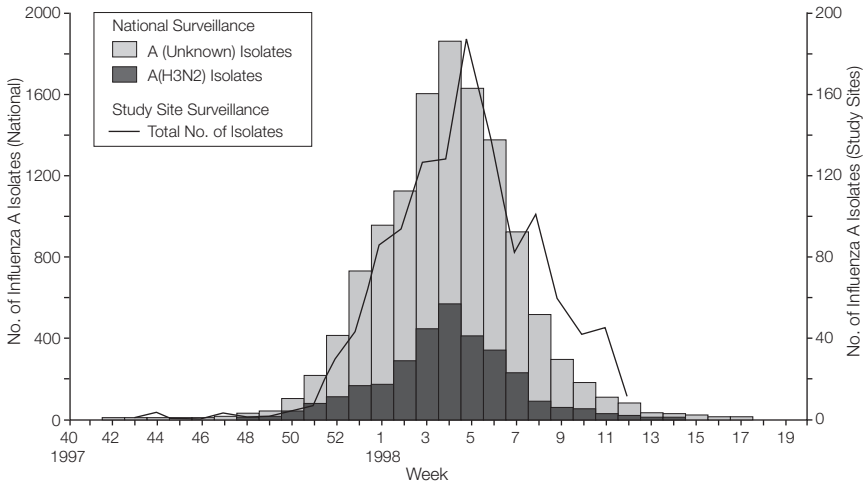
Because these benefits were observed during a season in which the pre-

Figure 2. Proportion of Study Participants Reporting 1 or More Days of Symptoms During the 7 Days Following Vaccination



Asterisks indicate symptoms for which the rate among vaccine recipients was significantly higher than among placebo recipients, with the upper limits of the 95% confidence intervals for the differences including or exceeding 10% (see "Methods" section of text). The rates of the other symptoms were equivalent between the groups. Fever was defined as an oral temperature of more than 37.8°C.

Figure 3. Weekly Influenza Surveillance for the 1997-1998 Influenza Season



Shown on the y-1 axis, with the bars, are the numbers of positive influenza type A isolates reported to the Centers for Disease Control and Prevention, Atlanta, Ga, by the World Health Organization collaborating laboratories in the United States (adapted from reference 22). Shown on the y-2 axis, with the line, are the numbers of positive influenza A isolates reported by the study site laboratories. Fewer than 1% of all influenza isolates during the 1997-1998 season were influenza type B isolates and were therefore omitted from the graph.

dominant circulating influenza virus strain, A/Sydney/05/97 (H3N2), was not well matched to the A(H3N2) strain contained in the vaccine, the findings suggest that LAIV provided cross-protection against the variant strain. During years with a better match between circulating viruses and vaccine strains, the effectiveness of trivalent LAIV might be even greater, although this has not been studied in adults. Cross-protection against the A/Sydney/05/97 (H3N2) variant during the 1997-1998 season was also demonstrated in a trial among children who received the intranasal LAIV vaccine.[23,24] Our trial did not compare LAIV vaccine with trivalent inactivated vaccine, and it is not known how the degree of cross-protection by LAIV against the A/Sydney/05/97 (H3N2) variant might compare with that afforded by trivalent inactivated influenza virus vaccine. However, several reports suggest that protection afforded by the trivalent inactivated influenza vaccine may have been poor during the 1997-1998 season.[21,25] Definitive information regarding the relative degree of cross-protection afforded by LAIV compared with inactivated vaccine, however, can be obtained only by directly comparing these vaccines in a clinical trial.

One possible mechanism for enhanced cross-protection might relate to the superior mucosal IgA and/or T-cell–mediated immune response induced by the LAIV vaccine.[9,12,13] Cytotoxic T cells may be cross-reactive against different subtypes of influenza A viruses because of their recognition of internal viral antigens expressed on the surfaces of infected cells that are shared among influenza A viruses, despite antigenic differences between the viral hemagglutinin molecules. The LAIV vaccine also may induce the production of more broadly cross-reactive humoral antibodies.[23]

Immunization with inactivated influenza virus vaccine can bring substantial health and economic benefits to healthy, working adults during years with a good vaccine-circulating virus strain match.[5,26-31] Our results confirm that the prevention of influenza in working populations reduces not only the burden of illness but also absenteeism and health care resource use. Consistent with national prescribing trends,[32,33] 30% of placebo recipients in our study who reported 1 or more febrile upper respiratory tract illnesses used prescription antibiotics (data not shown), despite the minimal benefits these medications have for most upper respiratory tract illnesses. The LAIV vaccine substantially reduced antibiotic use in our study. The prevention of influenza through vaccination may reduce unnecessary antibiotic use and thereby help control the emergence of antimicrobial resistance.

In our trial, recipients of the LAIV vaccine were more likely than placebo recipients to report runny nose and sore

Table 2. Numbers and Rates of Outcomes During Peak Outbreak Periods*

	Vaccine Group		Placebo Group			
	Total Outcomes, No. (n = 2833)	Rate per 1000 Persons per 7-Week Outbreak Period	Total Outcomes, No. (n = 1420)	Rate per 1000 Persons per 7-Week Outbreak Period	Reduction in Rates, % (95% CI)	*P* Value
Febrile illness						
Illness episodes, No.	406	151.3	225	168.1	10.0 (–2.1 to 20.7)	.10
Illness, d	3188	1188.0	2063	1541.2	22.9 (11.1 to 32.4)	<.001
Work missed because of illness, d	465	173.3	267	199.5	13.1 (–0.9 to 25.2)	.07
At least 1 health care provider visit, d	118	44.0	69	51.5	14.7 (–0.3 to 27.5)	.06
Taking antibiotics, d	525	195.6	459	342.9	42.9 (33.1 to 51.3)	<.001
Taking over-the-counter medications, d	1548	576.9	1007	752.3	23.3 (12.0 to 33.2)	<.001
Severe febrile illness						
Illness episodes, No.	298	111.0	183	136.7	18.8 (7.4 to 28.8)	.002
Illness, d	2740	1021.1	1880	1404.5	27.3 (16.7 to 36.5)	<.001
Work missed because of illness, d	415	154.6	252	188.3	17.9 (4.3 to 29.5)	.01
At least 1 health care provider visit, d	101	37.6	67	50.1	24.8 (11.6 to 36.1)	<.001
Taking antibiotics, d	462	172.2	435	325.0	47.0 (37.8 to 54.9)	<.001
Taking over-the-counter medications, d	1358	506.1	935	698.5	27.6 (16.5 to 37.1)	<.001
Febrile upper respiratory tract illness, d						
Illness episodes, d	248	92.4	162	121.0	23.6 (12.7 to 33.2)	<.001
Illness	2350	875.7	1559	1164.7	24.8 (13.5 to 34.7)	<.001
Work missed because of illness	287	107.0	200	149.4	28.4 (16.3 to 38.8)	<.001
At least 1 health care provider visit	64	23.8	54	40.3	40.9 (30.1 to 50.0)	<.001
Taking antibiotics	376	140.1	342	255.5	45.2 (35.2 to 53.6)	<.001
Taking over-the-counter medications	1186	442.0	822	614.1	28.0 (16.8 to 37.7)	<.001

*Data shown are event rates per 1000 subjects per 7-week period. Among vaccine recipients, 2833 participants provided information for 131 490 participant days. Among placebo recipients, 1420 participants provided information for 65 588 participant days. The rates were calculated as follows: rate = (counts/total participant days) × (7 days per week) × (7 weeks per outbreak period) × (1000 persons). CI indicates confidence interval. Peak outbreak periods were defined for each site according to the algorithm described in the "Methods" section of the text. See "Methods" section for definitions of illness categories.

throat during the week following vaccination. These symptoms usually lasted only 1 or 2 days and did not result in increased use of antibiotics, analgesics/antipyretics, or antihistamines/decongestants/antitussives. The 2 groups experienced equivalent rates of systemic symptoms, such as fever, headache, and muscle aches. Furthermore, there were no serious adverse events attributed to receipt of either vaccine or placebo in this study. Other studies have also demonstrated that bivalent and trivalent formulations of the vaccine may be associated with increases in mild upper respiratory tract symptoms but few, if any, other adverse effects.[17,18] Together, these studies confirm that LAIV vaccine is generally safe and well tolerated.

We used self-reported illness to evaluate vaccine effectiveness in this study. Self-reported respiratory tract illness can be highly reliable and valid compared with physician diagnoses.[34] Our illness definitions were selected to be highly sensitive and reflect findings that might be observed in daily clinical practice. Because our illness definitions did not have the level of specificity that might be obtained with laboratory confirmation of illness, our sample size was adjusted accordingly. However, given the event rates we observed in our study, our results suggest that the category of all febrile illnesses lacked sufficient specificity for us to demonstrate a significant difference in the proportion of participants experiencing illnesses. The illness definitions that incorporated a greater degree of severity or that required the presence of upper respiratory tract symptoms appeared to have greater specificity in our study.

Only persons for whom we had follow-up data were included in our analyses. For those lost to follow-up, we may have failed to capture important outcome information. However, the rates of nonresponse were low and equal in both groups, suggesting that the safety and effectiveness evaluations were unbiased.

In conclusion, influenza is a common cause of illness, absenteeism, and increased health care use in employed populations. Intranasally administered trivalent LAIV vaccine safely and effectively reduced these manifestations of influenza among healthy, working adults during a year in which a drifted influenza A virus predominated. These findings have potential implications for workers, their employers, and their health care providers.

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Table 3. Numbers and Rates of Outcomes During the Total Outbreak Period*

	Vaccine Group		Placebo Group			
	Total Outcomes, No. (n = 2874)	Rate per 1000 Persons per 14-Week Outbreak Period	Total Outcomes, No. (n = 1433)	Rate per 1000 Persons per 14-Week Outbreak Period	Reduction in Rates, % (95% CI)	*P* Value
Febrile illness						
Illness episodes, No.	751	276.5	412	302.5	8.6 (–2.0 to 18.0)	.11
Illness, d	6929	2551.3	3886	2853.1	10.6 (–0.7 to 20.6)	.07
Work missed because of illness, d	812	299.0	484	355.3	15.9 (3.9 to 26.4)	.01
At least 1 health care provider visit, d	213	78.4	128	94.0	16.5 (3.2 to 28.0)	.02
Taking antibiotics, d	1037	381.8	723	530.8	28.1 (16.6 to 38.0)	<.001
Taking over-the-counter medications, d	3163	1164.6	1846	1355.3	14.1 (2.7 to 24.1)	.02
Severe febrile illness						
Illness episodes, No.	543	199.9	326	239.3	16.5 (6.2 to 25.6)	.002
Illness, d	5945	2189.0	3473	2549.9	14.2 (2.8 to 24.2)	.02
Work missed because of illness, d	717	264.0	454	333.3	20.8 (9.2 to 30.9)	<.001
At least 1 health care provider visit, d	191	70.3	124	91.0	22.8 (10.3 to 33.4)	<.001
Taking antibiotics, d	957	352.4	684	502.2	29.8 (18.5 to 39.6)	<.001
Taking over-the-counter medications, d	2757	1015.2	1681	1234.2	17.7 (6.4 to 27.7)	.003
Febrile upper respiratory tract illness						
Illness episodes, No.	472	173.8	285	209.2	16.9 (6.5 to 26.2)	.002
Illness, d	5047	1858.4	2873	2109.4	11.9 (–0.1 to 22.4)	.05
Work missed because of illness, d	530	195.1	365	268.0	27.2 (16.1 to 36.8)	<.001
At least 1 health care provider visit, d	142	52.3	98	72.0	27.3 (15.2 to 37.7)	<.001
Taking antibiotics, d	793	292.0	553	406.0	28.1 (16.0 to 38.4)	<.001
Taking over-the-counter medications, d	2345	863.4	1483	1088.8	20.7 (9.7 to 30.4)	<.001

*Data shown are event rates per 1000 subjects per 14-week outbreak period. Among vaccine recipients, 2874 participants provided information for 266 154 participant days. Among placebo recipients, 1433 participants provided information for 133 480 participant days. The rates were calculated as follows: rate = (counts/total participant days) × (7 days per week) × (14 weeks per outbreak period) × (1000 persons). CI indicates confidence interval. The total outbreak period extended from December 14, 1997, through March 21, 1998. See "Methods" section of text for definitions of illness categories.

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