

ORIGINAL ARTICLE

Effectiveness of School-Based Influenza Vaccination

James C. King, Jr., M.D., Jeffrey J. Stoddard, M.D., Manjusha J. Gaglani, M.B., B.S.,
Kristine A. Moore, M.D., M.P.H., Laurence Magder, Ph.D.,
Elizabeth McClure, M.D., M.P.H., Judith D. Rubin, M.D., M.P.H.,
Janet A. Englund, M.D., and Kathleen Neuzil, M.D., M.P.H.

ABSTRACT

BACKGROUND

Vaccination of children in school is one strategy to reduce the spread of influenza in households and communities.

METHODS

We identified 11 demographically similar clusters of elementary schools in four states, consisting of one school we assigned to participate in a vaccination program (intervention school) and one or two schools that did not participate (control schools). During a predicted week of peak influenza activity in each state, all households with children in intervention and control schools were surveyed regarding demographic characteristics, influenza vaccination, and outcomes of influenza-like illness during the previous 7 days.

RESULTS

In all, 47% of students in intervention schools received live attenuated influenza vaccine. As compared with control-school households, intervention-school households had significantly fewer influenza-like symptoms and outcomes during the recall week. Paradoxically, intervention-school households (both children and adults) had higher rates of hospitalization per 100 persons than did control-school households. However, there was no difference in the overall hospitalization rates for children or adults in households with vaccinated children, as compared with those with unvaccinated children, regardless of study-group assignment. Rates of school absenteeism for any cause (based on school records) were not significantly different between intervention and control schools.

CONCLUSIONS

Most outcomes related to influenza-like illness were significantly lower in intervention-school households than in control-school households. (ClinicalTrials.gov number, NCT00192218.)

From the University of Maryland, Baltimore (J.C.K., L.M., J.D.R.); MedImmune, Gaithersburg, MD (J.J.S.); Scott and White Clinic, Texas A&M University, Temple (M.J.G.); University of Minnesota, Minneapolis (K.A.M., E.M.); and University of Washington, Seattle (J.A.E., K.N.). Address reprint requests to Dr. King at the Department of Pediatrics, University of Maryland School of Medicine, 737 W. Lombard St., Baltimore, MD 21201, or at jking@peds.umaryland.edu.

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CHILDREN ARE IMPORTANT VECTORS for the spread of influenza within households and communities.¹⁻⁶ Focusing efforts for influenza vaccination on healthy children may therefore be an effective and practical method of reducing the burden of influenza in the community.⁷⁻¹⁰ A recent pilot study demonstrated the feasibility of using trivalent, live attenuated influenza vaccine (FluMist, MedImmune) to vaccinate children in school and suggested there was a significant reduction in the rate of influenza-related outcomes in the households of children enrolled in the study.¹¹ The primary objective of our study was to assess the effect of a school-based vaccination program on the households of children attending the schools.

METHODS

CONTROL AND INTERVENTION SCHOOLS

We selected 24 public elementary schools in Maryland, Texas, and Minnesota and 4 parochial schools (kindergarten through eighth grade) in Washington state to participate in the study, to represent geographically and demographically diverse regions. Participating schools were grouped into clusters of two or three schools that were matched with respect to geographic characteristics and to students' ethnic background and socioeconomic status (according to the proportion of students receiving a subsidized lunch or tuition waiver). In each of the 11 clusters, one school was selected as the "intervention school" and was offered live attenuated influenza vaccine, and the other schools were designated as "control schools." The intervention school was selected randomly in seven of the clusters but designated by the school boards in the other four clusters (three in Maryland and one in Texas). School administrators in these four clusters would not accept a placebo-controlled or blinded study because of the disruption of class and staff time, with no benefit to pupils receiving placebo.

In the intervention schools, live attenuated influenza vaccine was offered at no charge to all healthy children 5 years or older in the fall of 2004. Members of households with children in either intervention schools or control schools could also receive influenza vaccination through their regular health care providers. The vaccine was administered according to its approved package insert.¹² Study nurses administered the 2004-

2005 formulation of the vaccine¹² intranasally to students during regular school hours. Children younger than 9 years who had never received the vaccine were offered a second dose 6 to 10 weeks after the first dose. The institutional review board of each participating center approved the protocol. Written informed consent was obtained from the parents or guardians of all children who received the vaccine in the intervention schools. In addition, assent was obtained from the older children.

COMMUNITY INFLUENZA SURVEILLANCE

The week of peak influenza activity early in 2005 was predicted for each state on the basis of results of influenza cultures, antigen tests, or both from regional medical center laboratories and physician offices and on the basis of surveillance data from the Centers for Disease Control and Prevention (CDC), to trigger the distribution of the household survey. Retrospective review of the local data was used to identify periods of influenza activity for analysis of school-based attendance. At the end of the influenza season, three outbreak periods were defined in each of the four study sites: the peak influenza week (defined as the week with the highest number of positive influenza tests), the influenza outbreak period (defined as the weeks before and after the peak week that had the next highest number of positive influenza tests until the total number of positive influenza tests was 85% or more of the season's total positive tests), and the intense influenza outbreak period (defined as the 4-week period encompassing the peak week, giving the highest number of patients with positive results).

HOUSEHOLD QUESTIONNAIRE

Immediately after the predicted peak week, all households with children in intervention and control schools received a questionnaire (see the Supplementary Appendix, available with the full text of this article at www.nejm.org). The anonymous questionnaire included questions about the demographic characteristics and influenza-vaccination status of household members. It also included questions about outcomes among household members from the previous week related to influenza-like illness, which was defined as fever or respiratory illness that included any one or more of the following symptoms: runny nose, nasal congestion, sinus problems, earache, ear infection, cough, sore throat, muscle aches, chills, or wheezing.

Questionnaires recorded the number of children and adults who had visited doctors or clinics, been hospitalized, taken medications, and missed days of school or work because of influenza-like illness.

SCHOOL ATTENDANCE

We collected data on absenteeism for any cause for each week of the academic year from each school. Within intervention schools, rates were also collected separately for students who had received the vaccine.

VACCINE-RELATED MEDICAL OUTCOMES

At the time of vaccination, parents of children who were about to receive the vaccine in an intervention school were questioned regarding the vaccinee's influenza-like symptoms, medication use, medically attended visits, and days of school lost, as well as paid days of work lost by a parent for the previous 7 days. This survey was repeated for the 7 days after the vaccination. Parents were advised to report to study coordinators any serious adverse events that occurred within 42 days after vaccination.

STATISTICAL ANALYSIS

To assess the primary objectives, we compared outcomes related to influenza-like illness of members of all households with children in intervention schools with those of households with children in control schools with respect to the rate of each of the outcomes collected in the questionnaire. We calculated these rates by determining the total number of events among household members (summing across households) and dividing by the total number of people in the households (also summing across households). To assess the statistical significance of observed differences and to control for differences in states and clusters, the data were analyzed with the use of linear mixed-effects regression models, using household-specific rates of each outcome as the dependent variables. The model included random effects for cluster and school and a fixed effect for state and intervention.

In an additional post hoc analysis, we compared households with children in elementary or middle school who received the vaccine with those with children who did not receive the vaccine across all outcomes, regardless of study-group assignment. The analytic approach was similar to that used for the primary objective.

A secondary objective was to assess the number of school absences with the use of administrative data from the schools. The change in absenteeism was calculated for each school between the weeks before influenza activity (September and October) and each predicted influenza outbreak period. These differences were used as dependent variables in a linear mixed-effects model, which included a random effect for the cluster and a fixed effect for the state. In intervention schools only, we calculated the difference in absentee rates between students who received the vaccine and students who did not receive the vaccine, by means of the paired t-test.

In an additional secondary analysis, we assessed the immediate effect of vaccination by comparing the responses to the survey administered at the time of vaccination with the responses provided 7 days later with respect to recent symptoms, medical care, school absenteeism, and workdays lost. The statistical significance of observed differences was assessed with the use of a generalized-estimating-equation approach¹³ to account for the correlation between repeated observations from the same person.

The original study design was proposed by the principal academic investigator and refined with input from the other authors (see the Supplementary Appendix for the contributions of specific authors). This study was sponsored by MedImmune. One of the investigators was employed by MedImmune at the time of the study and participated in the writing of the manuscript. The authors had complete and unfettered access to the data and vouch for the veracity and completeness of the data and analyses.

RESULTS

STUDY SCHOOLS

The intervention and control schools had similar characteristics (Table 1), including the number of students enrolled, the number of households, historical rates of absenteeism, ethnic background, and socioeconomic level.

VACCINE RECIPIENTS

A total of 2717 of 5840 students (47%) in intervention schools received the vaccine after parental consent (range, 30 to 56%). Of the 1535 eligible students, 95% received a second dose. Of the vaccinated students, 73% had received no previous

Table 1. Demographic Characteristics of Students and Their Households.*

Characteristic	Intervention Schools	Control Schools
Student data from school records		
Number of schools	11	17
Total student population (as of September 6, 2004)	5840	9451
Range of enrollment at all schools (September 6, 2004, to March 7, 2005)	174–969	189–998
Average number of households per school	384	412
Historical school absentee rates per student (days absent per 100 school days)		
2001–2002	4.3	4.0
2002–2003	4.4	4.2
2003–2004	4.2	4.0
Race or ethnic group — %		
White	68	70
Black	17	15
Hispanic	9	10
Asian	6	3
Other	2	1
Participation in school-lunch or tuition-waiver programs — %	34	34
Household data from questionnaires		
Questionnaires distributed — no.	4206	6952
Responses to questionnaires — no. (%)	3224 (77)	5763 (83)
Responses included in analysis — no. (%)	3022 (94)	5488 (95)
Race or ethnic group — %		
White	70	71
Black	11	10
Hispanic	7	7
Asian	3	2
Other	6	7
No response	3	2
Current vaccination with live attenuated influenza vaccine — %		
Adults	2	2
Infants	9	2
Elementary school students	45	2
Middle school students	15	2
High school students	3	2
Current vaccination for influenza (injection) — %		
Adults	11	11
Infants	17	16
Elementary school students	8	10
Middle school students	7	8
High school students	9	5
Households with an adult at home during school day — no. (%)	1571 (52)	2862 (52)
Adults working outside the home — no. (%)	4780 (79)	8616 (78)
Health insurance — %		
Private	66	62
Public	15	16
Other	16	18
None	4	5

* Percentages may not total 100 because of rounding. Race or ethnic group was reported by each school system.

influenza vaccination. The average age of vaccinated students was 7.9 years (range, 5 to 14). The ethnic background of vaccinated students was similar to that of the overall population of the intervention school.

IDENTIFICATION OF PEAK INFLUENZA WEEK

The peak influenza week was predicted correctly at two sites and was within 2 to 4 weeks at the other sites, as determined by retrospective surveillance data (Fig. 1). Of the positive specimens obtained, 75% tested positive for influenza A and 25% for influenza B. Nationally, the CDC reported predominantly influenza A (H3N2) isolates, the majority of which were A/California/7/2004, a drifted strain that was antigenically distinct from the influenza A (H3N2) strain in the vaccine.¹⁴

PRIMARY OUTCOMES

Questionnaires were returned by 77% of households with children in intervention schools and by 83% of households with children in control schools (Table 1). The number of reported episodes of influenza-like symptoms during the predicted peak influenza week was significantly lower in households with children in intervention schools than in households with children in control schools (Table 2). Reported rates of illness reflected rates for the entire household, which should not be confused with incidence rates based on reports of symptoms of individual household members. The number of reported episodes of fever plus cough or sore throat in children and adults in households with children in intervention schools was significantly lower than that in households with children in control schools ($P < 0.001$ for comparisons of both children and adults in each group). The use of prescription, over-the-counter, and herbal medications for influenza-like illness was significantly lower in households with children in intervention schools than in households with children in control schools ($P < 0.001$), as was the use of humidifiers ($P = 0.001$).

As compared with children in control-school households, children in intervention-school households had fewer visits to doctors or clinics for influenza-like illness ($P < 0.001$), and adults in these households had a trend toward fewer such visits ($P = 0.06$). The rates of emergency-room visits did not differ significantly between the groups. Members of intervention-school households (both children and adults) had higher rates of hospital-

ization per 100 persons than did those in control-school households (0.27 and 0.10 for children, respectively; $P = 0.03$; and 0.20 and 0.13 for adults, respectively; $P = 0.05$). However, the post hoc analyses comparing households with children who were vaccinated with those with children who were not vaccinated did not reveal a statistically significant difference in the number of hospitalizations for either children (0.20 per 100 persons for the vaccinated group vs. 0.10 per 100 persons for the unvaccinated group) or adults (0.15 per 100 persons for the vaccinated group vs. 0.15 per 100 persons for the unvaccinated group). Hospitalizations were reported at every site except Seattle (see the Supplementary Appendix).

As compared with households with children in control schools, households with children in intervention schools reported significantly lower absentee rates for influenza-like illness among students in elementary school ($P < 0.001$) and high school ($P = 0.03$) and significantly fewer workdays that were missed by parents to care for their own, or someone else's, influenza-like illness ($P = 0.04$).

Although 4 of the 11 intervention schools were not selected randomly, similar results were obtained when the analysis of data from the questionnaires was restricted to the randomized schools.

PRESPECIFIED SECONDARY ANALYSES

School Reports of Absenteeism

The change in absenteeism for any reason from baseline to the time of the defined influenza outbreak periods did not differ significantly between the two groups (Table 3). Both intervention and control schools had increases in the rates of overall absenteeism during the influenza outbreak (Fig. 1). Within intervention schools, unvaccinated students had a significantly greater increase in absentee rates over baseline than did vaccinated students for the predicted peak week ($P = 0.002$), the intense influenza outbreak period ($P = 0.01$), and the influenza outbreak period ($P = 0.006$).

Safety

Results from surveys taken both before and after the administration of the vaccine were consistent with previous experience with live attenuated influenza vaccine¹² (Table 2 of the Supplementary Appendix). In surveys taken after vaccination, students had significantly elevated rates of symptoms of influenza-like illness (with the exception of

wheezing) and use of nonprescription medicines and humidifiers than in surveys taken before vaccination. Vaccinated students had no significant increases in the use of prescription medications, visits to doctors or clinics, or missed days of school or work. No hospitalizations were reported among vaccinees in the first 7 days after vaccination. Four serious adverse events were noted in four students within 42 days after receiving the vaccine. These events included an episode of wheezing, shortness of breath, cough, and bronchospasm 4 days after vaccination in a 7-year-old, which was judged by an unblinded investigator as possibly related to the vaccine; the episode did not result in hospitalization. The other three events were judged either as not related or as probably not related to the vaccine by investigators who were aware of study-group assignments. These events included sore throat, nausea and vomiting, and fever with an elevated white-cell count 16 days after vaccination in a 7-year-old; gastroenteritis 1 day after vaccination in a 6-year-old; and an asthmatic exacerbation 36 days after vaccination in a 9-year-old. All events resolved completely.

DISCUSSION

This school-based vaccination intervention resulted in a reduction in influenza-related outcomes in household members of children attending intervention schools — a finding that was consistent with the results from an earlier pilot study.¹¹ Unlike traditional vaccine trials, this study was designed to compare the effect of school-based vaccination on schoolchildren and their household members regardless of the vaccination status of individual students. For this reason, the primary, prospectively defined analysis, which compared results in the intervention schools with those in the control schools (i.e., analysis by the unit of randomization), was the most appropriate measure. By comparing all children in control schools with all children in intervention schools (including those not vaccinated), we avoided potential confounding owing to differences between children who chose to be vaccinated and those who did not choose to be vaccinated. Children who did not receive the vaccine included those whose underlying medical conditions put them at risk for influenza-related complications.

The safety profile of live attenuated influenza vaccine in this study reveals a modest but statis-

Figure 1 (facing page). Relationship between Number of Positive Influenza Tests and School Absentee Rates in Intervention Schools and Control Schools during Key Periods of Influenza Outbreaks in Washington (Panel A), Minnesota (Panel B), Texas (Panel C), and Maryland (Panel D) in 2005, as Compared with Baseline Measures.

Baseline measures of absentee rates, which were obtained during an 8-week period in September and October 2004, are shown on the far left side of each panel, with numbers on the x axis indicating weeks of the year. The reference week of the questionnaire in early 2005 is indicated as a red number on the x axis in each panel. The peak week was defined as the week with the highest number of positive influenza tests. The influenza outbreak period was defined as the weeks before and after the peak week that had the next highest number of positive influenza tests until the total number of positive influenza tests was 85% or more of the season's total positive tests. The intense influenza outbreak period was defined as the 4-week period encompassing the peak week, giving the highest number of patients with positive results. CDC denotes Centers for Disease Control and Prevention.

tically significant increase in influenza-like symptoms and the use of nonprescription drugs after vaccination. However, these symptoms were probably mild because there were no significant increases in the use of prescription medications, visits to doctors or clinics, or school days or workdays lost by household members. There also was no increase in episodes of one of the most serious symptoms — wheezing. However, in accordance with the prescribing information for the vaccine, children with asthma were not knowingly vaccinated.

For feasibility reasons, our study was not placebo-controlled — a major limitation. Our primary outcome analysis relied on the anonymous household questionnaire. This questionnaire was more susceptible to bias than were the school-based absentee data, which were essentially blinded. The bias in responses to the questionnaire would probably be strongest in households with children in intervention schools who received the vaccine. The temporal separation between the vaccination effort in the fall of 2004 and the distribution of the questionnaires in February 2005 should have reduced this type of response bias.

In the secondary analysis, the school-based data on absenteeism did not confirm the differences observed in school absentee rates from data on the household questionnaires. Although the school-based data on absenteeism may be less subject to parental recall or selection bias than

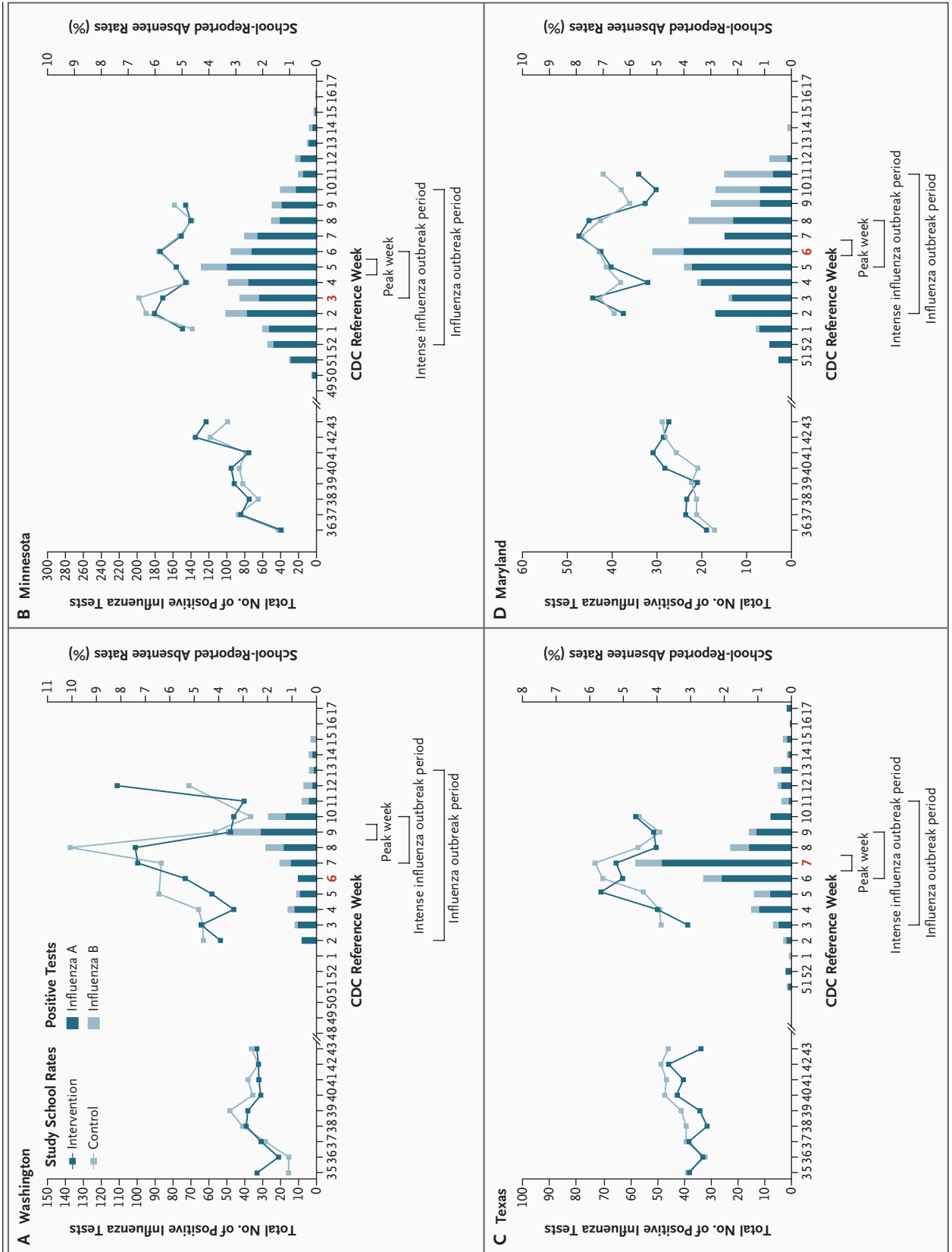


Table 2. Primary Analysis of Rates of Reported Use of Health Care and Medication, Missed Workdays, and School Absences Owing to Fever or Influenza-like Illness during the Peak Influenza Week, as Reported on the Household Questionnaire.*

Outcome	Intervention Schools	Control Schools	Adjusted Absolute Difference (95% CI)	P Value
Fever or influenza-like illness				
Total no. of households	3022	5,488	—	—
Children — no. (%)				
Any fever or influenza-like illness	1220 (40)	2,874 (52)	10.9 (8.4 to 13.3)	<0.001
Fever plus cough or sore throat†	512 (17)	1,446 (26)	8.3 (6.3 to 10.2)	<0.001
Adults — no. (%)				
Any fever or influenza-like illness	979 (32)	2,429 (44)	10.8 (8.0 to 13.6)	<0.001
Fever plus cough or sore throat†	253 (8)	710 (13)	3.7 (2.3 to 5.2)	<0.001
Use of health care				
Children — total no.				
Type of care — rate per 100 persons	7892	14,017	—	—
Outpatient (doctor's office or clinic)	7.27	11.37	3.39 (2.16 to 4.62)	<0.001
Emergency department or urgent care	1.03	1.32	0.24 (−0.22 to 0.70)	0.31
Inpatient	0.27	0.10	−0.13 (−0.25 to −0.01)	0.03
Adults — total no.				
Type of care — rate per 100 persons	6046	11,080	—	—
Outpatient (doctor's office or clinic)	4.96	6.70	1.12 (−0.04 to 2.28)	0.06
Emergency department or urgent care	0.89	0.97	−0.21 (−0.66 to 0.24)	0.36
Inpatient	0.20	0.13	−0.13 (−0.27 to 0.00)	0.05
Type of treatment				
Prescription — rate per 100 persons	7.27	11.70	3.71 (2.46 to 4.95)	<0.001
Over-the-counter — rate per 100 persons	17.43	25.26	7.71 (6.20 to 9.20)	<0.001
Vitamins or herbal remedies — rate per 100 persons	7.05	11.06	4.38 (3.06 to 5.69)	<0.001
Vaporizers or humidifiers — rate per 100 persons	4.39	5.88	1.69 (0.68 to 2.69)	0.001
School absence				
Any school-age children — rate per 100 persons				
Elementary school students	4.34	6.63	2.00 (1.27 to 2.73)	<0.001
Middle school students	4.37	7.00	2.35 (1.44 to 3.26)	<0.001
Middle school students	5.23	6.10	0.36 (−0.10 to 0.81)	0.63
High school students	3.46	5.75	1.73 (0.21 to 3.24)	0.03
Paid workdays missed by adults				
For any fever or influenza-like illness or to care for children with fever or influenza-like illness — mean no. of days	0.292	0.388	0.07 (0 to 0.14)	0.04
To care for sick child‡ — mean no. of days	0.202	0.264	0.05 (−0.01 to 0.10)	0.09

* The questionnaire was administered immediately after the predicted peak influenza week. Calculations of adjusted absolute differences and P values were based on a mixed-effects model, including random school and cluster effects and controlling for differences between states. Dashes denote that data are not applicable.

† The responses were from households reporting one or more children or adults with fever and one or more children or adults with either cough or sore throat.

‡ The responses were only from households in which no adults ordinarily stayed home during the school day.

are the household data, the data from the two sources are not directly comparable. The effects of an influenza vaccination program on absenteeism will be influenced by the percentage of the measured absenteeism owing to influenza, and the direct and indirect effects of the intervention. Although the questionnaire data included absences owing to influenza-like symptoms, the school-based attendance data included absences for any reason, thus possibly “diluting” the effects of influenza. In addition, the “direct” effects of the intervention on the outcome may have differed and would have depended on the relative percentage of vaccinees within a household or school. Finally, at the vaccination rates achieved in this study, the effects of indirect protection from influenza at the community level (herd immunity) may have occurred at the household level, but not at the school level. Although the precise reasons for the differences in results are not known, the public health implication is that vaccination of elementary schoolchildren may have an indirect effect on the occurrence of influenza-like illness within their own households.

The strength of this school-based intervention study is that it represents a population-level intervention. Even though fewer than half the children were vaccinated, important benefits were observed. We did not systematically collect information on reasons why families chose not to participate in the vaccination program. Nonetheless, the similarity of the populations of students and households is demonstrated by the close match in the demographic composition of the control and intervention schools. Sensitivity analysis of the questionnaire data did not reveal any notable differences in results between clusters in which the intervention school was or was not selected randomly. Community influenza surveillance allowed us to predict a week with high influenza activity during which household questionnaires could be distributed, which should have enhanced the specificity of outcomes related to influenza-like illness. In addition, surveillance allowed the precise delineation of influenza activity in the community retrospectively. However, the lack of culture-confirmed end points may have resulted in an underestimation of effectiveness, because measurement of nonspecific outcomes tends to underestimate effectiveness.¹⁵

The results of our primary analysis of data from questionnaires showed an increased rate of

Table 3. School-Reported Rates of Student Absenteeism for Any Reason, as Compared with Baseline.*

Absence	Intervention Schools		Control Schools		Difference between Baseline and Outbreak Period			
	Influenza Vaccine	No Influenza Vaccine	All Students	All Students	Influenza Vaccine vs. No Influenza Vaccine at Intervention School (95% CI)†	P Value‡	Intervention School vs. Control School (95% CI)	P Value‡
Baseline period	2.66	4.04	3.38	3.37	—	—	—	—
Peak week	4.04	7.20	5.71	6.04	1.8 (0.8 to 2.8)	0.002	0.2 (-0.4 to 0.8)	0.44
Intense influenza outbreak period	4.55	6.92	5.78	5.91	1.0 (0.3 to 1.7)	0.01	0.2 (-0.3 to 0.6)	0.47
Influenza outbreak period	4.27	6.50	5.44	5.56	0.8 (0.3 to 1.4)	0.006	0.2 (-0.2 to 0.6)	0.38

* The baseline was defined as an 8-week period in September and October 2004. The peak week was defined as the week with the highest number of positive influenza tests. The influenza outbreak period was defined as the period immediately before and after the peak week that had the next highest number of positive influenza tests until the total number of positive influenza tests was 85% or more of the season's total positive tests. The intense influenza outbreak period was defined as the 4-week period encompassing the peak week, giving the highest number of patients with positive results. Dashes denote that data are not applicable.

† P values were calculated by means of the paired t-test.

‡ P values were calculated with the use of a mixed-effects model, including cluster effects and controlling for state differences.

hospitalization for influenza-like illness among households with children in intervention schools, as compared with households with children in control schools. These data are contrary to other responses on the questionnaire. A post hoc analysis comparing households with vaccinated children and those with unvaccinated children indicated no significant difference in the rates of hospitalization in the two groups. This finding suggests that vaccination within the household was not the reason for the reported increased hospitalization for either children or adults. The post hoc analysis suggests that the results of the primary analysis of hospitalization rates are not robust. The questionnaire was not optimally designed to measure or characterize infrequent events, such as hospitalization, that we observed in this study. Nonetheless, it is difficult for us to understand why household members from intervention schools had an increased rate of hospitalization.

Previous studies have revealed reductions of various influenza-related outcomes in households or communities from interventions such as influenza vaccination of schoolchildren, prophylaxis with rimantadine, or the closing of schools during influenza outbreaks.^{8,16,17} A recent study conducted in Texas showed that herd immunity was associated with the use of live attenuated influ-

enza vaccine in children.¹⁸ Our multicenter study extends these observations and demonstrates that school-based immunization against influenza directly and indirectly reduces outcomes related to influenza-like illness.

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