ARTICLE

Influenza Vaccination Among College and University Students

Impact on Influenzalike Illness, Health Care Use, and Impaired School Performance

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Objective: To assess influenza vaccine effectiveness against influenzalike illness (ILI) and ILI impact on health care use and school performance among college and university students.

Design: Pooled analysis of 4 consecutive cohorts for the 2002-2003 through 2005-2006 seasons.

Setting: Twin Cities campus of the University of Minnesota (2002-2003 through 2005-2006 seasons) and St. Olaf College in Northfield, Minnesota (2005-2006 season).

Participants: Full-time students received e-mail invitations to participate in single-season cohorts. Internet-based surveys collected baseline (October) and follow-up (November-April) data.

Main Exposure: Influenza vaccination.

Main Outcome Measure: Proportion of students with ILI. Multivariable regression models assessed the effectiveness of vaccination for reducing ILI during months when influenza was circulating while controlling for confounders and after pooling data across the 4 cohorts.

Results: There were 2804, 2783, 3534, and 3674 participants in the 2002-2003, 2003-2004, 2004-2005, and 2005-2006 cohorts respectively, and overall, 30.2% were vaccinated. In the pooled analysis, 24.1% of students experienced at least 1 ILI during influenza seasons. Vaccination was associated with a significant reduction in the likelihood of ILI during influenza seasons (adjusted odds ratio, 0.70; 95% confidence interval, 0.56-0.89) but not during noninfluenza periods (adjusted odds ratio, 0.98; 95% confidence interval, 0.73-1.30). Vaccination was also associated with significant reductions in ILI-associated provider visits, antibiotic use, impaired school performance, and numbers of days of missed class, missed work, and illness during the influenza seasons.

Conclusions: Influenza vaccination was associated with substantial reductions in ILI and ILI-associated health care use and impairment of school performance. College and university students can experience substantial benefits from influenza vaccinations.

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ACUTE UPPER RESPIRATORY tract illnesses occur frequently among college and university students and are associated with substantial morbidity, including impaired school and work performance, increased health care use, and lower levels of general health.[1,2] Influenza viruses are among the common etiologic agents of upper respiratory tract illnesses in adults, accounting for 30% to 79% of febrile cough illnesses (influenzalike illnesses [ILIs]) in adults during influenza seasons.[3-7] In one study, about 28% of university students developed ILIs during the influenza season.[1] If one-third to three-quarters of these ILIs were caused by influenza, then the estimated incidence of influenza illness among these college and university students would be about 9% to 20%. Some reports of influenza outbreaks on college and university campuses have documented even higher rates of illness among the students.[8-10] Undoubtedly, influenza is common among college and university students, and its prevention might have an important impact on their health and well-being.

Previous studies of the benefits of influenza vaccination in healthy adult populations have often focused on employee-related outcomes, such as absenteeism and presenteeism. How these benefits might relate to students in college or university settings where class attendance and academic performance are important is unclear. We therefore undertook this study to assess the benefits of influenza vaccination in college and university students for reducing not only the incidence and severity of ILI and ILI-associated health care use, but also in reducing the impact of ILI on school performance.

METHODS

SETTINGS AND SURVEYS

The Burden of Respiratory Illnesses Among University and College Students Study represents a series of consecutive single-season cohorts involving students enrolled at the Twin Cities campus of the University of Minnesota (years 1-4) and expanded also to include St. Olaf College (a residential liberal arts college in Northfield, Minnesota) for year 4. All full-time students were invited by e-mail to participate in that year's cohort during October of each study year (2002-2003, 2003-2004, 2004-2005, and 2005-2006). Interested students were directed to a secure Internet site that contained detailed information about the study. Eligibility criteria included age 18 or older, full-time status, and anticipation of continuing enrollment through the end of the study period, October through April. Consenting students were assigned a unique pass code for use for completing the Internet-based baseline and follow-up surveys.

Participants completing the baseline surveys received monthly e-mail reminders to complete follow-up surveys for the months of November through April of the study year. The e-mail reminders were sent during the first week after the month of interest, with a second e-mail 1 week later to nonresponders. Subjects who completed all of the follow-up surveys were eligible to participate in random drawings for book store gift certificates (a $500 book store gift certificate for about every 1000 participants for year 1 and a $100 book store gift certificate for about every 200 participants for years 2-4). This study was approved by the human studies/institutional review boards of the participating institutions.

The baseline questionnaire asked about demographic and health characteristics of the participants. The follow-up surveys asked about occurrences of acute respiratory illness ($\geq$1 days of upper respiratory tract infection/common cold symptoms), symptoms (felt feverish, felt chilled, muscle aches, headache, sore throat, cough, runny nose, measured temperature >38°C), impact on daily life including school and work, health care use, and general health. Vaccination status was ascertained in the final survey to maximize completeness of vaccination status ascertainment because some students may have been vaccinated after November.

INFLUENZA SEASONS

Influenza seasons were defined retrospectively according to influenza surveillance data from the Minnesota Department of Health. Information on the specific types of circulating viruses for each season and the characterization of the degree of match between the predominant circulating viruses and vaccine strains was also obtained from influenza surveillance data from the Minnesota Department of Health.

OUTCOMES

The primary outcome was the proportion of students experiencing any ILI during the influenza seasons. Influenzalike illness was defined as 1 or more days of an acute respiratory illness associated with the symptoms fever/feverishness and cough. Other outcomes included days of ILI, ILI-associated days in bed and days with significant or minimal decrease in ability to perform usual activities, ILI-associated health care provider visits and antibiotic use, days of work and class missed because of ILI, ILI-associated impaired school performance (doing poorly in class, on a test, and on homework assignments), and days in the past month when physical health was not good because of any cause.

STATISTICAL ANALYSIS

Data for the 4 cohorts were pooled for the analyses to enhance statistical power. Descriptive comparisons between vaccinated and unvaccinated participants were conducted using χ^2 and t tests (SPSS for Windows, version 13; SPSS, Inc, Chicago, Illinois). Multivariable logistic regression (for categorical outcomes) and general linear models (for continuous outcomes) were used to assess the association of influenza vaccination with reductions in outcomes after controlling for important covariates and weighting for the number of months of follow-up data provided by each participant. Variables considered for inclusion in the models included all variables for which significant differences existed at baseline between vaccinated and unvaccinated persons in addition to year, school, vaccination status, and nature of vaccine-circulating influenza virus match for the predominant circulating strain for that season (good vs poor). Both forward and backward elimination procedures were used to identify the final models based on parsimony, overall predictive value, and consistency across the outcome measures. To test for evidence of bias in the study results, we also conducted analyses to compare the risk for ILI between vaccinated and unvaccinated persons during noninfluenza periods (the outcome months November-April that fell outside of the influenza season for that year). We hypothesized that if our multivariable models were functioning well, vaccinated and unvaccinated persons would have similar risks for ILI during the noninfluenza periods.

RESULTS

Nineteen thousand seven hundred ninety-six students volunteered to participate over the 4 study years by completing a baseline questionnaire, representing an estimated 12% to 15% volunteer rate each year from among the full-time student bodies. Of these, 17 998 (91%) completed at least 1 follow-up survey, including 12 975 (71% of the 17 998 and 65% of the 19 796) who provided information on their vaccination status. These 12 975 participants were included in the present analysis: 2804, 2783, 3534, and 3674 participants for the 2002-2003, 2003-2004, 2004-2005, and 2005-2006 cohorts, respectively (**Table 1**).

Baseline characteristics of the participants by cohort and vaccination status are shown in **Table 2**. Overall, 30.2% of participants were vaccinated. Vaccinated persons were somewhat older, more likely to be female, and to be high risk, whereas unvaccinated persons were more likely to smoke and to be undergraduates (Table 2). The clinical significance of these differences is unclear. Both groups completed similar numbers of follow-up surveys, with a mean of 5.7 of 6 for each group in the pooled analysis, representing about 95% of the follow-up surveys (Table 1).

The influenza seasons for each of the study years were defined as follows: January through March for the 2002-2003 and 2005-2006 seasons, December through February for the 2003-2004 season, and December through March for the 2004-2005 season.[11-15] The noninfluenza periods were therefore defined as including the months

Table 1. Detailed Response Information for Each Study Cohort

	2002-2003	2003-2004	2004-2005	2005-2006	Pooled
No. volunteering for study (filled out baseline questionnaire)	4935	4190	5224	5447	19 796
No. (%) who completed at least 1 follow-up questionnaire	4611 (93)	3812 (91)	4683 (90)	4892 (90)	17 998 (91)
No. who provided information on their vaccination status (and included in this study)	2804	2783	3534	3674	12 795
As % of all volunteers	57	66	68	67	65
As % of those completing at least 1 follow-up questionnaire	61	73	75	75	71
No. of monthly follow-up surveys completed (maximum of 6), of those who provided vaccination status information, %					
1	5.9	6.7	9.0	8.6	7.6
2	5.1	5.7	6.3	6.2	5.8
3	4.4	5.7	5.4	5.7	5.3
4	4.7	9.9	6.2	7.5	7.0
5	8.9	25.2	11.5	15.5	14.8
6	71.0	46.8	61.5	56.5	59.5
Mean % of monthly follow-up questionnaires completed among those who provided information on vaccination status	97.9	91.9	95.1	93.7	94.6

November, December, and April for the 2002-2003 and 2005-2006 cohorts; November, March, and April for the 2003-2004 cohort; and November and April for the 2004-2005 cohort. For all 4 influenza seasons, in Minnesota the predominant circulating viruses were A/H3N2 viruses. Each year's vaccine was well matched to these H3N2 viruses except for the 2003-2004 season in which the A/H3N2 vaccine component was poorly matched to that year's predominant circulating virus (A/H3N2/Fujian).[13]

Variables included in the final multivariable models included age, sex, high-risk status (having diabetes mellitus, asthma, or cardiac disease), current smoking status, general health level, undergraduate status, number of physician visits during the 6-month baseline period, year, and vaccine-virus match for the predominant circulating virus strain for that season. We also included interaction terms for year × vaccination and match × vaccination. For consistency, we used the same group of variables in each model.

Overall, 24.1% of students experienced an ILI during the influenza seasons. The rates of ILI and ILI-associated health care use and impaired school performance among vaccinated and unvaccinated participants and the association of vaccination with reductions in these outcomes are shown in **Table 3**. Vaccination was associated with a significant reduction in the proportion of participants experiencing ILIs during the influenza seasons (adjusted odds ratio [OR], 0.70; 95% confidence interval [CI], 0.56-0.89). Vaccination was also associated with significant reductions in the likelihood of having an ILI-associated physician or other health care provider visit, using antibiotics, and doing poorly in class or on an assignment. The mean number of days of illness and school and work loss because of ILI among vaccinated and unvaccinated students is shown in **Table 4**. Vaccination was associated with significant reductions in these outcomes as well. When averaged over the entire cohort, vaccination was associated with a reduction of 0.50 day of illness due to ILI per person vaccinated ($P < .001$). This translates into 1 day of ILI prevented for every 2 people vaccinated (Table 4).

During the 2003-2004 season with a poor match between the predominant circulating viruses and vaccine strains, vaccination was still associated with a significant reduction in ILI (adjusted OR, 0.69; 95% CI, 0.56-0.84).

For our analysis to detect bias, we compared the likelihood of ILI between vaccinated and unvaccinated participants for the influenza seasons and for the noninfluenza periods. We found that vaccinated and unvaccinated persons had a similar risk for ILI during the noninfluenza periods (adjusted OR, 0.98; 95% CI, 0.73-1.30) vs the significant reduction among vaccinated persons observed during the influenza seasons. These findings suggest that our multivariable models performed well and do not suggest significant bias.

COMMENT

In this study, we have demonstrated that influenza vaccination is associated with significant health and school performance benefits among college and university students. Previous studies of influenza vaccine effectiveness among younger adults have generally focused on working adults younger than 65 years. These studies have generally shown that vaccination reduces illness, health care use, and work absenteeism.[16-18] Our study extends previous observations by clarifying the benefits of vaccination specifically among college and university students. In addition to being associated with reductions in illness, health care use, and work absenteeism, vaccination was also associated with fewer episodes of school absenteeism and a lower risk for impaired academic performance.

Current influenza vaccines may be most effective when there is a good match between vaccine strains and circulating viruses. However, studies have also demonstrated substantial levels of protection during years when there is a poor match between circulating viruses and vaccine strains among healthy young adults,[18] healthy and high-risk adults aged 50 to 64 years,[19] and institutionalized elderly individuals.[20] The results of 2 additional trials that have included adults younger than 65 years and that were not included in the systematic review previously mentioned[18] have also found high levels of vaccine efficacy for poor-match seasons. One, a multiyear trial among

Table 2. Baseline Characteristics of Study Participants by Year and Influenza Vaccination Status

	2002-2003 (n=2804)		2003-2004 (n=2783)		2004-2005 (n=3534)		2005-2006 (n=3674)		Pooled (n=12 795)		
	VAC	UNVAC	VAC	UNVAC	VAC	UNVAC	VAC	UNVAC	VAC	UNVAC	*P* Value
No. of participants	728	2076	1152	1631	510	3024	1473	2201	3864	8932	
Age, y, mean (SD)	24.2 (7.5)	22.8 (7.2)	24.5 (7.3)	23.1 (6.2)	25.9 (8.0)	23.3 (5.5)	25.7 (8.3)	24.0 (6.6)	25.2 (7.9)	23.3 (6.3)	<.001
Male, %	26.9	29.6	24.3	31.5	24.1	29.2	26.3	28.1	25.5	29.4	<.001
No. of physician/health care professional visits in prior 6 mo, mean (SD)	2.4 (2.8)	2.2 (3.1)	2.4 (3.8)	2.0 (3.2)	3.2 (5.9)	12.0 (3.1)	2.4 (3.7)	2.0 (3.0)	2.5 (4.0)	2.0 (6.3)	<.001
Chronic medical conditions, %											
Diabetes mellitus	1.1	0.3	1.1	0.1	4.3	0.3	1.8	0.2	1.8	0.3	<.001
Asthma	10.3	8.1	10.9	6.7	17.8	6.0	11.1	6.6	11.8	6.7	<.001
Cardiac disease	0.9	0.4	0.5	0.3	1.0	0.4	0.7	0.4	0.7	0.4	.02
High risk[a]	11.8	8.6	12.1	6.9	21.8	6.6	13.3	7.0	13.8	7.2	<.001
Having a chronic medical condition requiring medication or regular physician visits	13.7	11.4	15.4	8.7	19.8	8.8	16.0	11.1	15.9	9.9	<.001
Current smoker, %	3.8	6.7	3.2	5.8	2.9	5.2	1.8	4.7	2.8	5.5	<.001
General health very good or excellent, %	66.5	60.0	67.6	63.4	65.7	64.4	68.0	62.8	67.4	63.3	<.001
Live on campus, %	35.4	34.1	28.1	30.8	26.5	29.9	30.8	35.2	30.3	32.3	.02
Undergraduate, %	55.9	70.4	52.1	68.0	42.5	63.0	47.2	62.0	49.7	65.4	<.001
No. of monthly follow-up surveys completed, mean (SD)	5.9 (0.43)	5.9 (0.49)	5.5 (0.76)	5.5 (0.80)	5 (0.63)	5.7 (0.76)	5.7 (0.72)	5.6 (0.85)	5.7 (0.69)	5.7 (0.75)	.37

Abbreviations: UNVAC, unvaccinated; VAC, vaccinated.
[a] High risk denotes having diabetes mellitus, asthma, or cardiac disease.

Table 3. Association of Influenza Vaccination With Reductions in the Likelihood of ILI and ILI-Associated Outcomes During Influenza Seasons[a]

	%			
Outcome	Observed Rates Among Vaccinated Participants (n=3663 Person-Seasons)	Observed Rates Among Unvaccinated Participants (n=8365 Person-Seasons)	Observed (Unadjusted) OR	Vaccine Effectiveness, Adjusted OR (95% CI)
≥1 ILIs	20.9	25.5	0.77	0.70 (0.56-0.89)
≥Health care provider visits because of ILI	5.7	6.7	0.85	0.53 (0.35-0.82)
Any antibiotic use because of ILI	3.4	4.3	0.78	0.54 (0.32-0.90)
Any missed class because of ILI	7.7	10.8	0.69	0.68 (0.45-1.02)
Do poorly in class because of ILI	9.0	11.7	0.75	0.67 (0.46-0.98)
Do poorly on an assignment because of ILI	8.4	11.4	0.71	0.60 (0.40-0.90)
Do poorly on a test because of ILI	4.3	5.9	0.71	0.53 (0.31-0.88)
Unable to do homework because of ILI	6.3	9.0	0.68	0.75 (0.48-1.17)

Abbreviations: CI, confidence interval; ILI, influenzalike illness; OR, odds ratio.
[a] N=12 028 persons-seasons. Data for the 4 cohorts have been pooled. Data have been weighted according to the number of follow-up months of data available for each participant. Shown are the results of the multivariable logistic regression analyses. See the "Methods" section of the text for details on variables included in the multivariable models.

persons 1 to 64 years of age (84% of subjects were between 16-64 years of age), found that inactivated vaccine efficacy against laboratory-confirmed influenza was 71% to 79% during the poor-match seasons and 74% to 79% during the good-match seasons.[21] Another controlled clinical trial among healthy adults in Michigan during the 2004-2005 season (nationally a poor-match year) demonstrated an inactivated vaccine efficacy against laboratory-confirmed influenza of 77%, a level within the 70% to 90% range typically seen during years with a good match.[22] In our study, we demonstrated significant vaccine effectiveness against ILI during the 2003-2004 season, which was a poor-match year in Minnesota. These findings underscore the potential benefits of vaccination even when there is not a good match between circulating viruses and vaccine strains.

We used upper respiratory tract illness associated with fever/feverishness and cough as the clinical case definition for ILI in our study. This is a nonspecific outcome, and we do not know the precise fraction of these ILIs that was caused by influenza viruses. It is likely, however, that 30% to 79% of these ILIs represented true influenza illnesses.[3-7] Previously published studies of influenza vaccine effectiveness have often used differing clinical case definitions. Given this heterogeneity of clinical case definitions that exists between published studies and the varying degrees of sensitivity and specificity for true influenza illness that can be associated with these different

Table 4. Association of Influenza Vaccination With Reductions in the Mean Number of Days of Illness Due to ILI and Days With ILI-Associated Impaired Work and Academic Activities During Influenza Seasons[a]

	Observed (Unadjusted) No. of Days per Participant, Mean (SD)		Observed (Unadjusted) Difference (Vaccinated vs Unvaccinated) in Mean No. of Days	Vaccine Effectiveness[b] (Adjusted) Difference (Vaccinated vs Unvaccinated) in Mean No. of Days (95% CI)	No. Needed to Vaccinate to Prevent 1 Outcome Day
	Vaccinated (n=3663 Person-Seasons)	Unvaccinated (n=8365 Person-Seasons)			
Missed class	0.18 (0.84)	0.28 (1.10)	−0.10	−0.06 (−0.10 to −0.02)	17
Missed work	0.21 (0.96)	0.29 (1.08)	−0.08	−0.09 (−0.13 to −0.05)	11
In bed	0.40 (1.38)	0.57 (1.65)	−0.17	−0.16 (−0.22 to −0.10)	6
With significant decrease in usual activities	0.89 (2.60)	1.20 (3.15)	−0.31	−0.26 (−0.38 to −0.14)	4
With minimal decrease in usual activities	0.83 (2.52)	1.09 (2.89)	−0.26	−0.22 (−0.32 to −0.11)	4.5
Until able to resume usual activities	1.09 (3.45)	1.45 (4.09)	−0.36	−0.35 (−0.51 to −0.20)	3
Ill	1.97 (5.09)	2.58 (5.89)	−0.61	−0.50 (−0.72 to −0.28)	2
Where physical health not good because of any cause	1.99 (5.04)	2.56 (5.84)	−0.57	−0.53 (−0.75 to −0.31)	2

Abbreviations: CI, confidence interval; ILI, influenzalike illness.
[a] N=12 028 persons-seasons. Data for the 4 cohorts have been pooled. Data have been weighted according to the number of follow-up months of data available for each participant. Shown are observed means for vaccinated and unvaccinated participants along with the results of multivariable general linear models regression analyses for estimating the difference in means.
[b] Difference represents rate in vaccinated minus unvaccinated after adjusting for all of the variables included in the multivariable models. A negative number indicates that vaccination was associated with a reduction in the outcome.

case definitions,[23] caution should be used in comparing our findings with the results of other studies, especially those that have used more specific outcomes, such as laboratory-confirmed influenza.

Many studies of influenza vaccine effectiveness have included only one or a few influenza seasons. Because of the variability of influenza from year to year, this can result in misleading results.[24] By pooling data from 4 influenza seasons, we were able to provide a longer-term view of the impact of ILI among college students and the benefits of vaccination that might be realized in this population.

All of our study data were collected through Internet-based surveys. This method facilitated access to large numbers of students and provided a convenient and minimally intrusive mechanism for participants to provide their monthly follow-up data. Other investigators have also successfully used e-mail[25] or Internet-based surveys[26,27] to assess ILI. Web-based surveys have been found to be reliable and to provide similar answers to questions administered through mailed questionnaires.[28]

Our study has several limitations. Because this is an observational study and not a randomized clinical trial, residual confounding may have biased our results.[29] We adjusted for important covariates in our multivariable models and also tested for bias by comparing the risk for outcomes between vaccinated and unvaccinated persons during influenza seasons and noninfluenza periods. Vaccinated and unvaccinated persons had similar rates of ILI during the noninfluenza periods, however, suggesting the absence of bias in our results. We also relied on self-report of vaccination status in our study. Self-report has been shown to have acceptable accuracy.[30,31] Nevertheless, we may have misclassified some of the participants according to vaccination status. Additionally, we did not collect information on the type of vaccine participants received, either trivalent inactivated or live attenuated vaccine. However, it is likely that most vaccinated participants received the inactivated vaccine as that was the vaccine offered during the institutions' vaccination programs each year (K.L.N., unpublished data, 2007). Finally, it is possible that our study subjects are not fully representative of college and university students across the country, and some caution should be used when applying our findings to other populations and settings. When compared with national data from the 2006 National College Health Association survey,[32] our study participants were somewhat more likely to be female (71.3% vs 63. 6%) and older (mean age, 23.7 vs 22.3 years). While the prevalence of asthma was somewhat less among our study participants (8.3% vs 11.2%), the rates of diabetes were close between the groups (0.7% vs 0.9%). Likewise, self-reported health levels were generally comparable between our study participants and the national survey respondents (64.2% excellent or very good in our study vs 62% from the national data).

Cold/flu/sore throat has been identified as the second leading cause of impediments to academic performance among college and university students across the United States.[32] Influenzalike illnesses undoubtedly are major contributors to this burden. In our study, we demonstrated that ILIs are common among college and university students and that they are associated with increased health care use, substantial decrements in health status, and impaired academic performance. Influenza vaccination was associated with significant reductions in the risk for ILIs during influenza seasons and with lower rates of health care use and impaired academic performance. Current recommendations for the prevention and control of influenza encourage vaccination for all persons 6 months and older who wish to reduce their risk of influenza illness.[33] Our findings highlight the kinds of benefits that could accrue to the nearly 18 million[34] college and university students in this country if they were vaccinated.

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The sooner patients can be removed from the depressing influence of general hospital life the more rapid their convalescence.
—Charles H. Mayo, quoted in *The Lancet*, 1916