Influenza Vaccine Effectiveness among Elderly Nursing Home Residents: A Cohort Study

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Outbreaks of influenza in nursing homes still occur, even when a large portion of residents have been inoculated with inactivated vaccine. Data were collected in 1991–1992 from 83 eligible skilled nursing homes located in southern Lower Michigan to determine the effectiveness of inactivated influenza vaccine in preventing influenza-like illness and influenza-associated pneumonia. Surveillance was conducted to identify the occurrence of influenza in the homes and, at the end of the season, specific data were gathered on all residents of homes with influenza activity. Age- and sex-adjusted estimates of vaccine effectiveness were calculated using Cox proportional hazards models for each nursing home. Estimates were pooled using precision-based weights calculated from data for each home. Vaccine was found to be 33% effective in preventing total respiratory illness (influenza-like illness and clinically diagnosed pneumonia). In prevention of pneumonia alone, vaccine was 43% effective. The estimate for prevention of pneumonia rose to 55% if the period under consideration was limited to the time of peak influenza activity. Given the number of eligible homes and the cohort methodology used, the results support continuation of current policy, encouraging use of vaccine in all nursing home residents. *Am J Epidemiol* 2001;154:155–60.

aged; influenza; nursing homes; vaccination

Although only a small portion of older individuals live in nursing homes, much of the literature on influenza in this age group describes outbreaks in such facilities (1–3). The reason for this apparent paradox involves more than the ease of recognition of disease in an environment with regular medical supervision. Nursing home residents are uniquely vulnerable to influenza morbidity and mortality. Although independently living older persons actually experience relatively low rates of clinical influenza compared with younger persons, this is not always true in the elderly residing in nursing homes. Once introduced into a facility, usually by staff or visitors, influenza can spread rapidly because of close contact among residents and because of their overall health status. The latter element is clearly involved in the severe manifestations of influenza illness, which can cause serious medical complications or death (4–6).

Influenza outbreaks occur even in nursing homes with high rates of vaccination in years when there is little difference between the circulating strain and the vaccine (7). Consequently, questions have been raised about its effectiveness, especially in the frail elderly who may not be able to mount an adequate immune response (8). This has even led to debate about using antivirals as a supplement to vaccination in these facilities (9). To examine the question of influenza vaccine effectiveness, we established a surveillance system for influenza and its complications in nursing homes located in southern Lower Michigan where a Health Care Financing Administration demonstration project was carried out. Thus, it was possible to follow outbreaks of influenza during three epidemic periods and to gather data on illnesses in the vaccinated and unvaccinated. A previous study was carried out in the first season using a case-control design. The effectiveness of vaccine in preventing influenza-like illness was estimated at 42 percent overall, with greater protection in those aged below 85 years. However, the case-control methodology limited the interpretation of the effectiveness of vaccine estimates (10). This report describes the determination of the effectiveness of influenza vaccination in preventing influenza-related illness and pneumonia among residents of these nursing homes during the final 1991–1992 influenza season when types A(H3N2) and A(H1N1) cocirculated (4). The prospective cohort methodology used allowed more direct estimation of vaccine effectiveness.

MATERIALS AND METHODS

Study area and influenza surveillance

The study area comprised seven counties in south-central and southwestern Lower Michigan. Located within the study area were 83 skilled nursing homes with an average bedsize of 100 beds (range, 56–357 beds). A community- and nursing home-based influenza surveillance program was carried out

from November through April in the period from 1989 to 1992 to determine the timing and etiology of influenza virus circulation. Medical practice sites and nursing homes reported weekly on the frequency of influenza-like illness (Centers for Disease Control and Prevention case definition of fever plus cough, sore throat, or nasal congestion) among patients or residents. Additional data on influenza virus activity were generated from the isolation results of throat culture specimens collected from persons who presented with symptoms of influenza-like illness. The methods of community surveillance have been reported previously as have the results of the nursing home studies of 1989–1990 (4, 7). In the nursing homes, data on incident febrile influenza-like or pneumonia illnesses specific to nursing home residents were recorded prospectively as part of infection control logs. Influenza was considered to have been introduced into a nursing home when at least 2 percent of residents developed influenza-like illness within a 7-day period during community-documented circulation of influenza, or when influenza was isolated from throat cultures collected from residents with influenza-like illness.

Study population and data collection

At the end of the surveillance period, representatives of nursing homes with evidence of influenza activity were invited to participate in a cohort study to evaluate the effectiveness of influenza vaccination in reducing the likelihood of influenza-like illness and its related complication, pneumonia. The study population was defined as all residents, aged 65 years and older, living in participating nursing homes on November 1, 1991, and for whom 1991–1992 influenza vaccination status was known.

To identify the study population, a census list was generated by each participating nursing home that included the initials, admission number and date, gender, and date of birth for every resident in the facility. Information on each resident's 1991–1992 influenza vaccination status and date of discharge, including discharge due to death or hospitalization, was collected from facility records. Residents younger than age 65 years, those with unknown influenza vaccination status, and those admitted after November 1, 1991, were excluded.

A list detailing every episode of influenza-like illness and/or pneumonia that occurred in each nursing home during the surveillance period was generated from infection control logs. All febrile illnesses had been prospectively entered into these logs, which had been retained for the purposes of this study. For each illness event, the resident's initials, admission number, type of illness (influenza like and/or pneumonia), and date of illness onset were recorded under supervision of a nurse-coordinator in each county. Admission numbers and initials were then used to match illness data to corresponding demographic, vaccination, and discharge information. All data collection was considered and approved by the University of Michigan Institutional Review Board.

Definitions of study variables

Influenza-like illness among residents was defined as an oral temperature (or rectal or axillary equivalent) of 37.8°C and one or more of the following signs or symptoms: cough, sore throat, or nasal congestion. This temperature has been used in previous studies and was chosen for its greater specificity than use of a lower cutoff (10). Pneumonia diagnoses were based on clinical diagnosis with or without radiographic confirmation. Episodes of influenza-like illness that progressed to pneumonia within 12 days or less were coded as pneumonia. In instances of multiple episodes of illness, the illness type and date of onset for the first illness event during the outbreak period were used in subsequent analyses.

Three endpoint measures were considered: total respiratory illness, pneumonia, and total respiratory illness-related death. Total respiratory illness included all cases of pneumonia and influenza-like illness that met the above case definitions. Total respiratory illness-related death included all deaths that occurred within 3 months of the date of onset of influenza-like illness or pneumonia.

Data analyses

Descriptive statistics, using t tests and chi-square techniques, were generated to characterize participating nursing homes by the proportion of vaccinated eligible residents and to evaluate any differences in population characteristics between vaccinated and unvaccinated residents and between those with and without reported influenza-like illness or pneumonia (11).

Illness rate ratios were calculated for the overall population and for individual nursing homes using Cox proportional hazards models (12). These models calculated point estimates for influenza vaccine effectiveness in reducing the likelihood of each of the three outcomes of interest and were adjusted for resident age and sex. This analytical method required illness outcomes in the vaccinated residents (vaccine failure) in each home for fitting of the Cox model and estimation of rate ratios. Using the results from the models for individual nursing homes, a pooled vaccine effectiveness estimate, or weighted average of the facility-specific estimates, was then computed as described by Haber et al. (13). The pooled estimate, weighted by the reciprocal of the variance of each point estimate, gave the highest weight to the most precise estimates. Therefore, the pooled estimate reflected the number of residents in each facility. Estimates of vaccine effectiveness derived from the proportional hazards models were equivalent to one minus the rate ratio (RR) ($(1 - RR) \times 100$). Pooled vaccine effectiveness estimates were calculated for the two time periods of interest, the entire period of influenza circulation from November 1, 1991, through February 29, 1992, and the 2-month period of peak influenza outbreak activity as determined by surveillance (peak period).

RESULTS

Surveillance

Data from community- and nursing home-based surveillance indicated that the months of December and January represented the periods of peak influenza circulation, while November plus February through April exhibited low or absent influenza activity (4). Both influenza A(H3N2) and

A(H1N1) cocirculated throughout the 1991–1992 epidemic period, with influenza A(H3N2) predominating (80 percent of all isolates). The antigenic characteristics of the circulating viruses were closely related to the vaccine strains (14).

Study population

Thirty nursing homes had evidence of introduction of influenza into their facilities and, in all 30, data were collected on their eligible residents. In preliminary analyses, four small (23–45 eligible residents) nursing homes whose residents had high rates of vaccination (87–96 percent vaccinated) reported no illness outcomes among the unvaccinated. Since recorded illness in the unvaccinated persons was required for calculation of appropriate rate ratios, these four homes were excluded, and all subsequent analyses were limited to the remaining 26 homes. The eligible population in the 26 homes numbered 2,351 residents, with the number of those eligible by home ranging from 37 to 156 residents. The mean and median age of the resident population was 85 years; the ages ranged from 65 to 106 years. Seventy-eight percent of the eligible residents were women. Overall, 74 percent of the residents were vaccinated prior to the influenza season; this value varied significantly by nursing home and ranged from 40 to 97 percent ($p < 0.001$). Men and women were equally likely to be vaccinated (74 percent vs. 73 percent, $p = 0.73$) and, although the likelihood of vaccination increased with age, the proportion vaccinated did not vary significantly by 5-year age categories ($p = 0.18$). Other variables, such as heart and lung disease, which may predict vaccine use and require adjustment in an open population, were not significantly associated with vaccination in these nursing homes. As shown in table 1, male resi-

dents were significantly more likely than female residents to experience any respiratory illness (RR = 1.30; 95 percent confidence interval: 1.08, 1.56), pneumonia (RR = 2.02; 95 percent confidence interval: 1.38, 2.97), and death within 3 months of respiratory illness (RR = 2.50; 95 percent confidence interval: 1.66, 3.79). Although the likelihood of respiratory illness and death within 3 months of respiratory illness increased with age, these relations were not statistically significant.

Influenza vaccine effectiveness estimates

In bivariate analyses (unadjusted) (table 2), vaccinated residents were significantly less likely to have experienced any respiratory illness (RR = 0.81; 95 percent confidence interval: 0.68, 0.97) or pneumonia (RR = 0.57; 95 percent confidence interval: 0.39, 0.84). Death within 3 months of respiratory illness was not significantly less likely among the vaccinated (RR = 0.77; 95 percent confidence interval: 0.50, 1.20).

Because chi-square tests for homogeneity did not reject the null hypothesis (all p values > 0.75) that vaccine effectiveness estimates are constant across nursing home sites, pooled estimates could be calculated for all major outcome variables. Table 2 presents the estimates of vaccine effectiveness from the Cox proportional hazards model for both the overall study population (unweighted estimates) and after pooling results calculated for each home (weighted estimates). All models were adjusted for resident age category and sex. Both unweighted and pooled rate ratios for influenza vaccination suggested significantly reduced likelihood of total respiratory illness (RR = 0.73; 95 percent confidence interval: 0.60, 0.89 and RR = 0.67; 95 percent

TABLE 1. Number, percentage, and rate ratio for influenza vaccination status, resident age category, and gender with illness outcomes including total respiratory illness, pneumonia, and death within 3 months of respiratory illness onset ($n = 2,351$), southern Lower Michigan, 1991–1992

	Total respiratory illness (451 events)			Pneumonia (106 events)			Death within 3 months of illness (88 events)		
	No.	%	RR*	No.	%	RR	No.	%	RR
Influenza vaccination									
Yes	312	18.1	0.81	65	3.8	0.57	60	3.5	0.77
No	139	22.3		41	6.6		28	4.5	
Age category (years)									
65–69 (ref)†	10	10.8		2	2.2		2	2.2	
70–74	30	16.2	1.51	7	3.8	1.76	5	2.7	1.26
75–79	56	17.5	1.63	14	4.4	2.03	9	2.8	1.31
80–84	99	18.9	1.76	22	4.2	1.96	19	3.6	1.69
85–89	109	19.3	1.79	22	3.9	1.81	23	4.1	1.89
90–94	90	20.9	1.94	25	5.8	2.70	15	3.5	1.62
>94	57	24.4	2.26	14	6.0	2.78	15	6.4	2.98
Gender									
Female	332	18.0		68	3.7		52	2.8	
Male	119	23.4	1.30	38	7.5	2.02	36	7.1	2.50

* RR, crude unadjusted rate ratio.
† ref, reference category.

TABLE 2. Comparison of rate ratio estimates, unweighted and weighted for nursing home site, of influenza vaccine effectiveness in reducing the likelihood of total respiratory illness, pneumonia, and death within 3 months of respiratory illness onset among elderly nursing home residents during the entire study period (*n* = 2,351), southern Lower Michigan, 1991–1992

	Adjusted, unweighted estimate*		Adjusted, pooled (weighted) estimate†	
	Rate ratio	95% Confidence interval	Rate ratio	95% Confidence interval
Total respiratory illness	0.73	0.60, 0.89	0.67	0.54, 0.83
Pneumonia	0.52	0.35, 0.76	0.57	0.36, 0.89
Death within 3 months of illness	0.70	0.45, 1.10	0.68	0.14, 1.18

* Results from Cox proportional hazards models of overall population adjusted for resident age category and gender.

† Results from calculation of pooled vaccine effectiveness estimates across multiple Cox models (26 individual nursing homes) adjusted for resident age category and gender.

confidence interval: 0.54, 0.83, respectively) and pneumonia (RR = 0.52; 95 percent confidence interval: 0.35, 0.76 and RR = 0.57; 95 percent confidence interval: 0.36, 0.89, respectively) for vaccinated residents. Death within 3 months of respiratory illness onset was less likely among the vaccinated. However, neither estimate was statistically significant.

Table 3 presents summary derivations ((1 – RR) × 100) of influenza vaccine effectiveness in reducing the likelihood of total respiratory illness, pneumonia, and death within 3 months of illness, for the entire period of influenza activity as used above and for the more narrow period of peak influenza activity. For the outcomes total respiratory illness and pneumonia, estimates of vaccine effectiveness were improved for the peak period, suggesting that precision of these case definitions had been improved. For the peak period, the estimate of vaccine effectiveness was 34.5 percent in preventing total respiratory illness, and for the more narrowly defined outcome, pneumonia effectiveness was 54.7 percent. Deaths were reduced by 31.7 percent in the entire period, but this was not statistically significant. Because of small numbers, it was not possible to evaluate deaths during shorter periods.

DISCUSSION

Inactivated influenza vaccine has been strongly recommended for many years for annual use in all persons aged 65 years and older. This recommendation was based on the demonstration of efficacy in repeated randomized trials conducted in younger persons (15). Because there had never been a similar demonstration of efficacy in older persons and because outbreaks of influenza continued to occur among residents of nursing homes with high rates of vaccination, questions have been raised as to whether the vaccine was effective in the elderly. For ethical reasons randomized trials could not be conducted in the United States in older persons, since it would mean denying vaccine to those who received placebo. As a result only observational studies could be conducted. Several studies that used either case-control or cohort methodology (16–19) were carried out in independently living populations. The outcome was usually hospitalization due to a diagnosis of pneumonia and influenza, but other outcomes were studied as well. These studies, although of varying designs, demonstrated vaccine effectiveness in the range of 31–55 percent. However, they all involved the independently living elderly, who are generally younger and healthier than those in nursing homes. Thus, the controversy regarding effectiveness among nursing home residents continued, in spite of a single study that indicated that vaccine, although similar in effectiveness in preventing influenza-like illness, was even more effective in preventing associated pneumonia and death (20).

The current study presents results from the final year of a 3-year influenza vaccine effectiveness study in nursing

TABLE 3. Summary of adjusted, pooled influenza vaccine effectiveness estimates ((1 – rate ratio) × 100) for prevention of total respiratory illness, pneumonia, and death within 3 months of illness onset among elderly nursing home residents during the entire season of influenza activity (*n* = 2,351) and the peak outbreak period (*n* = 2,274), southern Lower Michigan, 1991–1992

Endpoint	No. of events	Study period	Pooled estimate of effectiveness (1 – RR*)	95% Confidence interval (1 – RR)
Total respiratory illness	451	Total season	33.1	16.7, 46.3
Total respiratory illness	325	Peak period	34.5	15.1, 49.5
Pneumonia	106	Total season	43.3	10.7, 64.0
Pneumonia	64	Peak period	54.7	20.1, 74.4
Death within 3 months of total respiratory illness	88	Total season	31.7	–21.4, 61.5

* Cox proportional hazards models with calculation of pooled rate ratio estimates (RRs) across 26 nursing homes and calculation of vaccine effectiveness estimates ((1 – rate ratio) × 100).

homes that were selected to be representative of facilities in the region. In the first year, in which there was major type A(H3N2) activity, the case-control design was used to estimate vaccine effectiveness. In that study, the adjusted odds ratio of 0.58 (95 percent confidence interval: 0.43, 0.78; $p < 0.001$) indicated a vaccine effectiveness estimate in preventing influenza-like illness among nursing home residents of 42 percent (10). However, questions remained about the interpretation of these results because of methodological issues, including the use of a case-control design for a frequent outcome. In this study it was found that the factors, such as underlying chronic respiratory and cardiac disease, that confounded studies of effectiveness in independently living populations of older persons were not of importance in nursing homes. In the second year, there were no outbreaks of influenza in the homes, so vaccine effectiveness could not be computed. In the current study or third year, both A(H3N2) and A(H1N1) viruses circulated in the community. A(H3N2) predominated and, as expected, was the subtype more involved in the nursing homes. Data were collected so that a cohort design could be used to estimate vaccine effectiveness with Cox proportional hazards models. Use of the Cox proportional hazards model provides on unbiased measure of direct protection of vaccine (21). Unlike the previous case-control method, the proportional hazards model measures the relative risk of the outcome of interest in infinitesimally small time intervals under the assumption that the relative risk is constant over the study period (22). Another assumption includes occurrence in a closed, randomly mixing population, where a single outbreak results in immunity. Other assumptions are that the population is closed, randomly mixing, with a single outbreak resulting in immunity. If unvaccinated residents mix preferentially together, one might expect a higher transmission probability in this group. However, most of the nursing homes were small (73 percent under 100 residents) so this is not likely to have been a problem.

Two vaccine effectiveness estimates were computed using the Cox proportional hazards model. These were the overall study population estimates (adjusted/unweighted) and the estimates pooled across individual nursing homes (adjusted/weighted). The overall study population estimates were computed using an aggregate analysis combining data from the 26 nursing homes. This overall vaccine effectiveness estimate indicated a significant decrease in the risk of development of influenza-like illness and pneumonia among the vaccinated. The definition used for influenza-like illness was a standard one; pneumonia is difficult to diagnose uniformly in this setting, in which radiographic examinations are not routinely performed. Thus, the clinical diagnosis was used.

In these closed and often highly vaccinated populations, a question that needs to be considered is whether the demonstrated effectiveness is a result of individual or direct (individual) protection or indirect protection, a result of herd immunity. Serie et al. (23) observed varied attack rates among the vaccinated and unvaccinated residents in different areas of a geriatric hospital and attributed the observed differences to herd immunity. In this study, there were dif-

ferences in the number of study participants per home (range, 37–156 residents) and vaccination rates per home (range, 40–97 percent). These differences may have contributed to differences in herd immunity across nursing homes, and, in fact, four homes with high rates of vaccination among residents had to be excluded from analysis because of zero attack rates among the unvaccinated. However, the Cox model controls for exposure to infection and should account for differences in herd immunity.

In the current study, tests for homogeneity did not detect departures from homogenous vaccine effects across nursing homes, and thus, pooled estimates were calculated as described by Haber et al. (13). The pooled vaccine effectiveness estimate demonstrated a significant decrease in the risk of development of influenza-like illness and pneumonia among the vaccinated. Vaccinated residents were 33 percent and 43 percent less likely to develop influenza-like illness and pneumonia, respectively, adjusting for age and gender, during the whole influenza season. The pooled vaccine effectiveness estimate was higher during the peak outbreak period than during the entire study period. Peak period effectiveness estimates were 35 percent and 55 percent for the prevention of influenza-like illness and pneumonia, respectively. This increase is likely related to a reduction of misclassification in the diagnosis of influenza-like illness during this peak period. There was a higher frequency of influenza virus isolation in the community and in the nursing homes during the peak outbreak period, indicating that influenza was the etiologic agent involved. The comparability of the results of this study with those of the first year confirms the point estimates of vaccine efficacy calculated in this study. In fact, given the different methodology and the different years involved, the consistency strengthens the conclusion of vaccine effectiveness as do previous results from a period when much less vaccine was used in nursing homes (20). They are all likely underestimates, as are the results of studies in the independently living, because the individual cases were not classified by virologic techniques.

Influenza vaccination of nursing home residents provides significant protection in preventing influenza-like illness and pneumonia. Different methods have demonstrated significant protection, although probably less in those over age 84 years than in younger persons (10). Certainly it would be desirable if they produced higher levels of protection, which indicates once again the need for improved vaccines. However, the existing vaccines appear valuable even in preventing influenza-like illness. The previous studies demonstrated the importance of existing vaccines in preventing death that, although not statistically significant in the current analysis, was reduced by 32 percent (20). By extension, it would be expected that the vaccine would be effective in preventing other life-threatening complications as was actually suggested in this study. Thus, the present policy should be supported and extended to prevent introduction of influenza through vaccination of nursing home staff and appropriate use of antivirals, including the new neuraminidase inhibitors, either as adjuncts to vaccination or to terminate outbreaks once they begin (9, 24).

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