Reduced Hospitalizations and Death Associated With Influenza Vaccination Among Patients With and Without Diabetes

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OBJECTIVE — To assess whether the influenza vaccination of community-dwelling, diabetic, elderly individuals is associated with reduced rates of hospitalization and death.

RESEARCH DESIGN AND METHODS — In this outcome-research study, we compared mortality and hospitalization rates of 15,556 patients aged ≥65 years followed using a diabetes registry in a large health maintenance organization to that of 69,097 members not suffering from chronic disease who were considered as a reference group. The study outcomes included all-cause death and hospitalization in internal medicine or geriatric wards for any reason over winter and summer (control) periods.

RESULTS — Vaccination rates were 48.8 and 42.0% among patients with diabetes and the reference population, respectively. Influenza vaccination was associated with a 12.3% reduction in hospitalization rates for patients with diabetes compared with 23.0% in the reference group ($P = 0.08$). The reduction in hospitalization rates was similar in both sexes among patients with diabetes. In addition, there was a significant reduction in mortality for the vaccinated group of patients with diabetes when compared with the nonvaccinated group except for female patients aged ≥85 years.

CONCLUSIONS — The study results support the use of influenza vaccine among an elderly population. However, there does not appear to be an additional benefit for patients with diabetes.

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Serious complications of influenza among the elderly include pneumonia and exacerbations of coexisting conditions that can result in hospitalization and death (1). Vaccination against influenza has consistently been associated with reductions in hospitalizations for pneumonia and death from all causes in the elderly (2,3). It has been shown that vaccination of high-risk groups (e.g., patients with diabetes, renal disease, rheumatological disease, dementia, and stroke) reduced hospitalizations for respiratory conditions by 39% (4). In addition, the effectiveness of the influenza vaccine in reducing hospitalization due to cardiovascular and cerebrovascular causes and death from any reason has also been demonstrated (5).

The few observational studies of diabetic subjects demonstrated up to 79% reduction in hospitalization rates (6,7). Although these studies were based on a small sample, they were sufficient for the Centers for Disease Control and Prevention to recommend inoculation with influenza vaccine for diabetic patients (8). Studies of the immunological responses have shown that influenza vaccine elicits comparable antibody responses in people with diabetes and control subjects (9,10) The aims of the current study were to assess whether the influenza vaccination of community-dwelling, diabetic, elderly individuals is associated with reduced rates of hospitalization and death.

RESEARCH DESIGN AND METHODS

— Maccabi Healthcare Services (MHS) is the second largest preferred provider organization in Israel, insuring 1.6 million members nationwide. According to the Israeli National Health Insurance Act of 1994, MHS is obliged to insure every citizen who wishes to join it, irrespective of age, sex, physical condition, or any other criterion. Therefore, every section in the Israeli population is represented in MHS.

MHS has developed and implemented a computerized information system fully employed in all levels of the organization. Demographic and clinical data are collected in real time from all levels of care and stored on a central database.

We compared the rate of vaccination and hospitalization of those diabetic patients included in our diabetes register (11) with that of the other HMS members not suffering from chronic disease (the low-risk group). This low-risk group, which was our reference group, was identified in a manner similar to that used by Nichol et al. (4). All MHS members who were at least 65 years of age on 1 October 2000 were included in the study and had been continuously enrolled in MHS during the preceding 12 months and throughout the outcome period. The MHS diabetes register is computer based and has been continuously updated from

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Abbreviations: MHS, Maccabi Healthcare Services.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

1999. The following entry criteria are used: *1)* HbA_{1c} ≥7.25%; *2)* glucose ≥200 mg/dl (for individuals that are included in the register on this criterion alone, supporting data for the diagnosis of diabetes is required at 6 months; if none are found, the patient is deleted from the register); *3)* purchase of diabetes medication twice in the previous 2 months; and *4)* a diagnosis of diabetes (ICD-9 code) in the chart and HbA_{1c} ≥6.5% or glucose >125 mg/dl. These criteria have been validated and give a specificity of 99.9%. All MHS members are offered free annual influenza vaccinations, and pneumococcal vaccines are offered in addition at no charge on a one-time basis to those patients that have not previously received this vaccination.

Vaccination status

Influenza vaccination status was ascertained from the database. The rate of one-time pneumococcal vaccine uptake, which is offered to all MHS members from the age of 65 years, was extracted from the database for the 5 years before the study year.

Data collection

MHS has a nationwide network of over 3,000 independent physicians and clinics that use the MHS medical practice computer system. Computerized patient consultation and prescription records are downloaded daily to a central computer. In addition, the database is automatically updated with every hospitalization, specialist visit, non–over-the-counter drug purchase, laboratory tests, imaging tests, nursing, physiotherapy treatment, and other treatments. These data are aggregated to the level of the individual member using the member's unique identity number. Demographic data (e.g., age and sex) and diagnoses were obtained from the MHS administrative and clinical databases. Baseline coexisting conditions were defined by inpatient or outpatient diagnoses using the ICD-9 clinical modification codes. Diabetic patients were identified using Maccabi's diabetes register. The low-risk group was defined by the absence of any of one of the following conditions: heart disease, lung disease, diabetes or endocrine disorders, renal disease, stroke or dementia, vasculitis, rheumatologic disease, or cancer.

The study outcomes included hospitalization in internal medicine and geriatric wards for any reason or death. Admission data are sent to Maccabi by the hospitals for the purpose of billing and are therefore complete.

Statistical analysis

Study outcomes between diabetic and low-risk patients were compared. Proportions of sex and prevalence rates were compared using χ^2 test corrected for continuity, and mean age was compared using standard Student's *t* test. Significance values and 95% CIs were calculated using Compare2 version 1.11 (copyright J.H. Abramson 2000–2002).

The rate of hospitalization was studied over the months of October through February. A control period lasting from June through September was selected. We did not expect the vaccination to provide benefit during this control period because in the summer months there is a vastly reduced prevalence of Influenza in Israel.

RESULTS

— Vaccination rates were 48.8 and 42.0% among 15,556 patients with diabetes and 69,097 in the reference group (elderly subjects with no chronic disease), respectively. The average age ± SD of vaccinated and nonvaccinated patients was similar among patients with diabetes 72.8 ± 0.6 and 73.1 ± 0.5 years, respectively, as well as among nondiabetic subjects 74.7 ± 0.8 and 74.2 ± 0.5 years, respectively. Women comprised 48.2 and 53.4% of vaccinated patients with and without diabetes, respectively, and 57.9 and 59.6% of unvaccinated patients with and without diabetes, respectively.

Patients with diabetes who were vaccinated showed a 12.2% decrease in rate of hospitalization when compared with nonvaccinated diabetic patients. The nondiabetic patients who were vaccinated showed a 23% decrease in rate of hospitalization when compared with nonvaccinated nondiabetic patients. However, these differences in the protective effect of influenza vaccination between the diabetic and reference group were of borderline statistical significance ($P = 0.08$).

As expected, no significant differences were found between vaccinated and nonvaccinated patients in hospitalization rates during summer time. Among reference patients, hospitalization rates were 6.55 and 5.98% for vaccinated and nonvaccinated, respectively. Among patients with diabetes rates were 5.84 and 5.61% for vaccinated and nonvaccinated, respectively. In contrast to this, group comparison of hospitalization rates during winter among reference patients showed substantial differences between vaccinated and nonvaccinated at 6.99 and 9.08%, respectively (OR 0.75 [95% CI 0.75–0.80]). Among vaccinated and nonvaccinated patients with diabetes, hospitalization rates were 8.29 and 9.44%, respectively (0.87 [0.77–0.97]).

The rate of one-time vaccination with pneumococcal vaccination between the diabetic and reference group was 20.3% (95% CI19.7–20.8) and 19% (18.7–19.3), respectively.

The rate of hospitalization during the summer months among the patients with diabetes that had been vaccinated was 6.6%, as opposed to 6.0% (OR 0.90 [95% CI 0.79–1.03]) in those not vaccinated. This compares with 5.8 and 5.6%, respectively, in the reference group (1.05 [0.98–1.12]). Table 1 describes the hospitalization rates for patients with diabetes and the reference group by vaccination status, age, and sex during the winter and summer periods. Overall, increased hospitalization rates were obtained during winter time, increasing with age and for male patients. While among reference patients influenza vaccination was associated with significant reduction in hospitalization rates for all age and sex categories examined, patients suffering from diabetes showed a more moderate benefit. In some patients (e.g., males aged 65–75 yes), no reduction was observed.

The mortality rate (Table 2) of vaccinated as opposed to unvaccinated men was 1.2 and 3.1% (OR 0.35 [95% CI 0.25–0.49]), respectively. The mortality rate of vaccinated as opposed to unvaccinated women was 0.6 and 2.6% (0.32 [0.20–0.50]), respectively. Among men, the relative reduction in mortality increased with age. The rate of vaccination among men was 54.53% as opposed to 45.86% among women.

CONCLUSIONS

— This study clearly supports the use of annual influenza vaccination in elderly patients. The decrease in rate of admission (23%) in our reference group is similar to that of other studies, such as that described by Nichol et al. (4) who found a 29% reduction. A previous smaller case reference study of Colquhoun et al. (6) compared the vaccination status of in-patients with diabetes with matched nonadmitted patients in the community during an epidemic of influ-

Table 1—*Hospitalization rates among diabetic patients and low-risk patients with and without influenza vaccination during winter and summer periods (2000–2001) and corresponding OR and 95% CI, stratified for age and sex*

		Not vaccinated		Vaccinated			95% CI	
Age (years)	Diabetes	Hospitalizations (*n*)	Rate (%)	Hospitalizations (*n*)	Rate (%)	OR	Low	High
Winter								
Men								
65–75	No	649	6.2	434	5.4	0.87	0.77	0.99
	Yes	195	8.0	205	7.9	0.99	0.81	1.22
75–85	No	539	13.0	474	10.7	0.81	0.71	0.92
	Yes	101	12.8	121	10.5	0.80	0.60	1.05
>85	No	372	24.3	193	17.6	0.66	0.55	0.81
	Yes	22	18.8	18	10.1	0.48	0.25	0.95
Women								
65–75	No	658	5.1	355	3.8	0.74	0.65	0.85
	Yes	225	7.5	155	6.5	0.85	0.68	1.04
75–85	No	836	10.8	395	7.8	0.70	0.62	0.79
	Yes	166	12.0	111	9.7	0.79	0.61	1.02
>85	No	586	18.2	176	15.1	0.80	0.67	0.96
	Yes	43	17.7	19	16.5	0.92	0.51	1.66
Summer								
Men								
65–75	No	410	3.90	353	4.42	1.14	0.98	1.32
	Yes	125	5.10	141	5.43	1.07	0.83	1.37
75–85	No	348	8.40	372	8.43	1.00	0.86	1.17
	Yes	68	8.65	86	7.47	0.85	0.61	1.19
>85	No	207	13.51	162	14.74	1.11	0.89	1.38
	Yes	12	10.26	20	11.17	1.10	0.52	2.35
Women								
65–75	No	417	3.22	306	3.31	1.03	0.88	1.19
	Yes	156	5.23	123	5.12	0.98	0.77	1.25
75–85	No	505	6.53	342	6.76	1.04	0.90	1.20
	Yes	117	8.45	76	6.65	0.77	0.57	1.04
>85	No	361	11.19	157	13.44	1.23	1.01	1.51
	Yes	44	18.11	8	6.96	0.34	0.15	0.74

enza and found a 79% reduction of admissions among diabetic patients who were vaccinated, which is much higher than our entire population study that was not undertaken during an epidemic. This may have been due to the small number of index cases (80) and the fact that there was an influenza epidemic. Our study was undertaken for an entire population of 15,556 patients with diabetes over a representative winter period without a clear-cut influenza epidemic.

In contrast to previous studies, we found a smaller relative reduction in hospitalization among vaccinated patients with diabetes when compared with a reference population. One possible confounder could have been a difference in the rate of pneumococcal vaccine uptake between these populations. The rate of pneumococcal vaccination in patients with diabetes was slightly greater than that of the reference population. Pneumococcal vaccination might have been expected to further reduce rates of admission of the diabetic patients and thus may support the conclusion that influenza vaccine is not more effective in the diabetic than in the reference population. A further explanation for the relative reduced effectiveness may be the higher baseline admission rate for patients with diabetes, as indicated in the summer period. Hospitalization data were not gathered from wards other than internal medicine and geriatrics because we assumed that the rate of admission to the other wards would be less dependant on the season and less relevant for infectious disease. In winter, patients with diabetes can be admitted for other reasons than influenza. This applies both in patients with and without diabetes and is thus unlikely to effect the overall conclusions.

From the summer period data, it is evident that our vaccinated population of diabetic patients is a slightly sicker population than the nonvaccinated diabetic patients, with 10% more admissions during the summer months that cannot be related to influenza.

Interestingly, there was a significant difference in vaccination rates between the sexes. This is consistent with previous findings (12). The mortality data suggest a profound protective effect of vaccination. For men, this increases with age. However for women >85 years of age we did not find a protective effect for mortality or hospitalizations. This is probably due to the smaller number of subjects in this age group.

Due to its design, this study suffers from a number of weaknesses such as lack of cause of hospitalization, lack of classification between type 1 and type 2 diabe-

Table 2—*Mortality among diabetic patients with and without influenza vaccination during winter 2000–2001 and corresponding OR and 95% CI, stratified for age and sex*

Age (years)	Vaccine	*n*	No. of deaths	Mortality rate (%)	OR	95%CI Low	95%CI High	*P*
Men								
65–75	No	2,467	39	1.6%	1*			
	Yes	2,728	16	0.6%	0.37	0.21	0.66	<0.001
75–85	No	932	50	5.4%	1*			
	Yes	1,346	27	2.0%	0.36	0.224	0.58	<0.001
>85	No	207	22	10.6%	1*			
	Yes	249	8	3.2%	0.28	0.12	0.64	<0.001
Overall	No	3606	111	3.1%	1*			
	Yes	4323	51	1.2%	0.35	0.25	0.49	<0.001
Women								
65–75	No	2,749	37	1.3%	1*			
	Yes	2,466	13	0.5%	0.39	0.21	0.73	<0.001
75–85	No	1,459	53	3.6%	1*			
	Yes	1,254	4	0.3%	0.09	0.03	0.24	<0.001
>85	No	369	28	7.6%	1*			
	Yes	157	7	4.5%	0.57	0.24	1.33	0.13
Overall	No	4,577	118	2.6%	1*			
	Yes	3,877	24	0.6%	0.32	0.20	0.50	<0.001

*Reference category.

tes, and lack of detailed information regarding comorbidity. Since vaccination is only carried out by our nurses using a unique patient identity number and since this elderly population is unlikely to receive a vaccination in a place of work, misclassification of vaccination status is unlikely.

In summary, this data clearly shows that influenza vaccination reduces hospitalization and death among elderly patients and clearly supports efforts to increase the rate of annual influenza vaccination.

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