Influenza Vaccination of Health Care Workers in Long-Term-Care Hospitals Reduces the Mortality of Elderly Patients

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Vaccination of health care workers (HCWs) is recommended as a strategy for preventing influenza in elderly patients in long-term care. However, there have been no controlled studies to show whether this approach is effective. During the winter of 1994–1995, 1059 patients in 12 geriatric medical long-term-care sites, randomized for vaccination of HCWs, were studied. In hospitals where HCWs were offered vaccination, 653 (61%) of 1078 were vaccinated. Vaccination of HCWs was associated with reductions in total patient mortality from 17% to 10% (odds ratio [OR], 0.56; 95% confidence interval [CI], 0.40–0.80) and in influenza-like illness (OR, 0.57; 95% CI, 0.34–0.94). Vaccination of patients was not associated with significant effects on mortality (OR, 1.15; 95% CI, 0.81–1.64). Results of this study support recommendations for vaccination against influenza of HCWs in long-term geriatric care. Vaccination of frail elderly long-term-care patients may not give clinically worthwhile benefits.

The Centers for Disease Control and Prevention (CDC) in the United States and departments of health in the United Kingdom (UK) strongly recommend influenza vaccination for elderly people who have chronic disease or who are resident in long-term-care institutions [1, 2]. The main benefits claimed after vaccination are a reduced risk of influenza and of influenza-associated pneumonia, which can be life-threatening.

Grouping frail elderly people in institutions may create an environment that facilitates the rapid spread of influenza. Comparison of elderly people who accept vaccine with those who refuse have shown that vaccination is associated with a reduction in pneumonia or death [3]. Similar results have been reported in case-control studies of those dying of influenza [4]. Despite this, many specialists in geriatric medicine in the UK are skeptical of the value of routine influenza vaccination; in a survey, <20% said they offered it to elderly people in their long-term-care wards [5]. There are reasons why influenza vaccine may not be effective in this group. Institutionalized elderly people often have severe and debilitating chronic disease [6] in association with undernutrition [7]. Such persons often have impaired immune function and may not develop adequate protective circulating antibody concentrations after influenza vaccination [8, 9].

Vaccination of health care workers (HCWs) has been suggested as an additional strategy that might reduce the carriage and transmission of influenza [10]. Although the CDC recommends this approach in care environments where patients have an increased risk of complications of influenza [1], there are no controlled studies to show its efficacy.

The aims of this study were to determine whether vaccination of HCWs looking after patients in geriatric medical long-term care and vaccination of long-term-care patients reduces the patient incidence of influenza, lower respiratory tract infection, and death.

Methods

Study groups. We studied 1059 patients (302 were men) resident on 31 October 1994 in 12 geriatric medical long-term-care hospitals in Glasgow. The number of patients per site ranged between 55 and 119. Hospital policies of vaccinating or not vaccinating patients were maintained as per usual practice. Six hospitals had an "opt-out" policy, in which patients were routinely given influenza vaccine unless they refused or had a major contraindication. Six hospitals had an "opt-in" policy, in which patients were given vaccine only if they or their relatives requested it following ward advertisement of the availability of influenza vaccine. Hospital sites were stratified by unit policy for vaccination, then randomized for their HCWs to be routinely offered either influenza vaccination or no vaccination. This resulted in 4 hospital groups: staff

Received 7 May 1996; revised 20 August 1996.

Presented in part: British Geriatrics Society meeting, London, 13 October 1995 (Potter J, Stott DJ, Roberts MA, et al. Influenza vaccination of patients and healthcare workers in geriatric medical long-term care [abstract]. Age Ageing 1996;25:28).

This study was approved by the relevant local hospital ethical committees. Written informed consent was obtained from health care workers who received influenza vaccine as part of the study. Surveillance of patients comprised careful recording of usual clinical practices; verbal consent was obtained before blood and nasopharyngeal aspirate samples were taken.

Financial support: Greater Glasgow Health Board Care of the Elderly Unit; Medeva.

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The Journal of Infectious Diseases 1997;175:1–6

0022–1899/97/7501–0001$01.00

and patients unvaccinated (S0P0), staff vaccinated and patients unvaccinated (SVP0), staff unvaccinated and patients vaccinated (S0PV), and both staff and patients vaccinated (SVPV).

Vaccination of patients and HCWs began in October 1994 (4 weeks before the earliest likely start date of the annual influenza outbreak). HCW vaccinations were given by trained occupational health nurses. All HCWs working in hospital groups SVPV and SVP0 were included (day and night nurses and nursing auxiliaries, ward cleaners, doctors, therapists, and porters). Voluntary workers, patients' friends and relatives, and other casual or occasional ward visitors were not offered vaccine. Of 1078 HCWs identified at these sites, 653 (61%) agreed to participate and received influenza vaccine. Vaccination was contraindicated in 34 HCWs (3%), and 47 (4%) were on long-term sick leave and were unavailable.

Methods of measurement and follow-up. Patients had their primary diagnoses recorded and physical dependency measured using the 20-point Barthel activities of daily living index [11]. A venous blood sample (10 mL) was taken from all consenting patients before vaccination and at the end of the study for assay of influenza A and B antibody by single radial hemolysis, using antigen from the 1993–1994 season (on advice of the National Institute of Biological Standards and Control, Potters Bar, UK), which was closely related to the 1994–1995 strain. Rising titers of antibodies to *Mycoplasma pneumoniae* were sought by complement fixation test. Blood samples have been analyzed only from unvaccinated patients in groups SVP0 and S0P0. Vaccinated patients have not been included, as a rise in influenza antibody titer could be due to either vaccination or infection.

Between the end of October 1994 and the end of March 1995 (5 months), patients were monitored for symptoms or signs of influenza-like illness or lower respiratory tract infection. All deaths were recorded (including date and certified cause of death), as were all discharges from and admissions to the wards. The surveillance of patients was organized as follows: The ward nurses were asked to notify 1 of 2 research nurses (by radiopage or answering machine) if any patients under their care developed clinical symptoms suggestive of upper respiratory tract viral illness, influenza, or lower respiratory tract infection. The research nurse then visited the patient (within 24 h of referral) to record symptoms, clinical signs, and results of available relevant investigations using standardized forms. Chest radiographs were not included as part of the routine assessment of suspected lower respiratory tract infection, as for many of the peripheral hospitals, it would have required an ambulance journey for the patient.

Patients with suspected viral illness who gave verbal consent had a nasopharyngeal aspirate (NPA) sample obtained within 48 h of notification of symptoms. IFA for influenza A and B, respiratory syncytial virus (RSV), *Chlamydia psittaci,* and adenovirus antigens in epithelial cells was done using kits (Dako, High Wycombe, UK). Patients were revisited by the research nurses 2–3 days later to assess, by standard means, possible development of lower respiratory tract infection.

Disease definitions. Influenza-like illness was defined as temperature $\geq$37.0°C plus one or more of the following symptoms: new-onset cough, coryza, sore throat, malaise, headache, or muscle pains [12]. Lower respiratory tract infection was identified by the presence of (1) pulmonary crackles, wheeze, or tachypnea plus temperature $\geq$37.0°C or white blood cell count $>10 \times 10^9$/L or (2) a positive sputum culture.

Statistical analysis. Statistical analyses were done using the SPSS statistical software. Baseline characteristics, morbidity, and mortality in the 4 groups of hospitals were compared using the χ^2 test, unpaired Student's t test, and Wilcoxon rank sum test as appropriate. Odds ratios and 95% confidence intervals were calculated [13] for the effects of staff and patient vaccination. Survival analysis was by Kaplan-Meier product limit estimates, using the Tarone Ware test for statistical significance. Cluster analysis, examining mortality rates and other outcomes by hospital site, was also done [14]. $P < .05$ was considered statistically significant.

Results

The characteristics of the 4 patient groups are shown in table 1. There were no significant differences in the proportions of men and women (χ^2 test) or mean ages (unpaired t test) between the different groups. The Barthel score was lower in hospital sites where patients were routinely offered vaccine (SVPV and S0PV) than in sites where patients were not routinely vaccinated (SVP0 and S0P0; Wilcoxon rank sum test, $P = .003$). There was no significant difference in Barthel score between hospital sites where HCWs were vaccinated (SVPV and SVP0) compared with sites where HCWs were not vaccinated (S0PV and S0P0). Only 1 patient (0.2%) was vaccinated in a hospital with a policy of not routinely offering patients vaccination, compared with 478 (88.8%) in hospitals with routine patient-vaccination policies.

There were significant differences in mortality between the 4 patient groups (table 2, $\chi^2 = 11.46$, $P < .01$). Vaccination of HCWs was associated with a reduction in total patient mortality from 17% (S0PV and S0P0) to 10% (SVPV and SVP0; figure 1A, table 3). This difference remained statistically significant in a cluster analysis by hospital site ($t = 3.03$, 10 *df,* two-tailed $P = .013$). There was no significant difference in mortality between hospital sites whose patients were offered vaccine (SVPV and S0PV) and those whose patients were not (SVP0 and S0P0; figure 1B, table 3; cluster analysis, $t = -1.12$, 10 *df,* $P = .29$). In a stepwise multivariate analysis (including age, sex, hospital staff vaccination status, hospital policy for vaccination of patients, patient vaccination, and Barthel score), nonvaccination of HCWs ($P < .001$), Barthel score ($P = .004$), and age ($P = .03$) were significantly associated with increased patient mortality, whereas a hospital policy for nonvaccination of patients was not ($P = .33$).

The proportions of patients developing suspected viral illness or influenza-like illness were significantly reduced in hospitals where HCWs were vaccinated (table 3). There was a tendency for the incidence to be lowest in sites where HCW and patients were offered vaccine (SVPV). HCW or patient vaccination had no statistically significant effects on the risk of patients developing lower respiratory tract infection; however, the numbers of patients fulfilling the criteria were small and the confidence intervals wide.

Table 1. Characteristics of the patient study groups in the influenza vaccination study.

	SVPV	SVP0	S0PV	S0P0
No. of study patients	230	260	308	261
Sex, male:female	58:172	82:178	83:225	79:182
Age, mean (SD) years	78.4 (19.7)	76.6 (22.1)	75.2 (23.4)	78.5 (19.7)
Median Barthel score (25th, 75th centiles)	3 (2, 6)	4 (2, 8)	3 (2, 6)	4 (2, 9)
No. (%) of study patients vaccinated	195 (84.8)	1 (0.4)	283 (91.9)	0
Vaccinated:unvaccinated staff	293:147	362:276	—	—

NOTE. SVPV, staff-vaccinated patients-vaccinated sites; SVP0, staff-vaccinated patients-unvaccinated sites; S0PV, staff-unvaccinated patients-vaccinated sites; S0P0, staff-unvaccinated patients-unvaccinated sites.

Paired serum samples were obtained from 225 (43%) of 521 unvaccinated patients. Many patients refused a blood sample, and paired samples were available only from survivors (n = 454). A significant rise in antibody titer to influenza A was found in 2 of 107 paired serum samples from patients in group S0P0 compared with 3 of 118 in group SVP0. Serologic evidence for influenza B infection was found in 4 of 107 in group S0P0 compared with 2 of 118 in group SVP0. No patient had a rise in antibody titer to *M. pneumoniae.* Of 212 NPAs, none were positive for either influenza A or B or *C. psittaci,* 14 were positive for RSV, and 11 were positive for adenovirus.

Discussion

Vaccination of HCWs in geriatric medical long-term care was associated with a reduced rate of patient mortality and influenza-like illness. Previous studies have shown that up to 25% of HCWs can be infected with influenza virus during the winter months [15]. HCWs may potentially both import the virus into long-term-care wards and act as a vector for its circulation. In our program, vaccination of HCWs was achieved in 61%. Work done in our departments has shown that <3% of HCWs in acute-care hospital sites in Glasgow received influenza vaccine in 1993 [16]. Given the current UK national guidelines that vaccination of HCWs is specifically not recommended, it is likely that only a very few HCWs in our study would have obtained influenza vaccine otherwise.

We did not attempt to vaccinate voluntary workers, patients' friends or relatives, or other casual ward visitors. It is possible that such groups could act as a source of influenza, bringing the virus into the wards and infecting patients, thus undermining a program of vaccination of carers. However, our data suggest that by concentrating on vaccination of the paid ward staff, benefits can be obtained for the patients. The vaccination program included the group with the closest and most intimate contact with patients, the ward nurses. In view of the nature of their work, this group may be the most likely to pass influenza to patients in long-term care.

In our study, seroconversion to influenza A or B occurred in 5% of unvaccinated surviving patients, and no patients with suspected respiratory tract illnesses had a positive NPA for influenza. The numbers of patients with virologically confirmed influenza were therefore small, and it was not possible to demonstrate the presence or absence of an association between

Table 2. Mortality, influenza-like illness, and lower respiratory tract infection in the patient study groups.

	SVPV	SVP0	S0PV	S0P0
Study patients	230	260	308	261
Deaths	25 (10.9)	25 (9.6)	56 (18.2)	42 (16.1)
Deaths associated with pneumonia	10 (4.3)	15 (5.8)	24 (7.8)	23 (8.8)
Episodes of suspected viral illness	24	58	75	59
Temperature ≥37.0°C	2 (8.3)	22 (37.9)	21 (28)	24 (40.7)
Cough	11 (45.8)	34 (58.6)	42 (56)	38 (64.4)
Coryza	7 (29.2)	24 (41.4)	27 (36)	29 (49.2)
Sore throat	5 (20.8)	11 (19)	21 (28)	12 (20.3)
Malaise	6 (25)	33 (56.9)	33 (44)	32 (34.3)
Headache	3 (12.5)	5 (8.6)	5 (6.6)	5 (8.5)
Muscle pains	2 (8.3)	5 (8.6)	5 (6.6)	8 (13.5)
Patients developing influenza-like illness	2 (0.9)	20 (7.7)	19 (6.2)	23 (8.8)
Patients developing lower respiratory tract infection	7 (3.0)	14 (5.4)	16 (5.2)	18 (6.9)

NOTE. Data are no. (%). SVPV, staff-vaccinated patients-vaccinated sites; SVP0, staff-vaccinated patients-unvaccinated sites; S0PV, staff-unvaccinated patients-vaccinated sites; S0P0, staff-unvaccinated patients-unvaccinated sites.

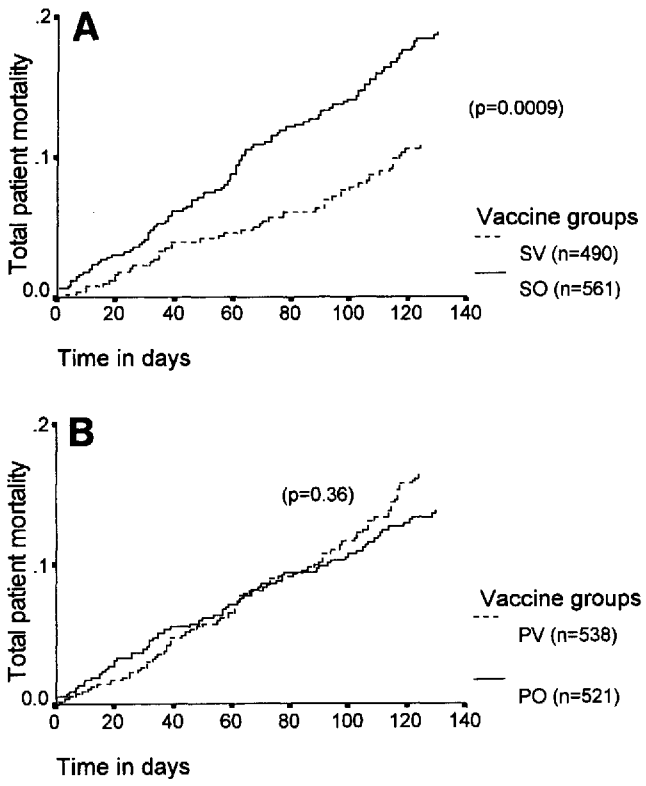

Figure 1. Total patient mortality (proportion of all patients) in **A**, geriatric long-term-care hospital sites where HCWs were offered influenza vaccine (SV) compared with sites where they were not offered vaccine (S0), and **B**, hospital sites where patients were routinely given vaccine (opt-out policy, PV) compared with sites where they were not routinely vaccinated (opt-in policy, P0). Time course is from 31 October 1994 (time 0).

nonvaccination of HCWs and virologically proven influenza among patients. Therefore, we do not have any direct evidence that the reductions in rates of patient mortality and influenza-like illness that were associated with HCW vaccination were due to prevention of influenza.

Although only a small proportion of our patients could be shown to have had influenza, this is consistent with circulation of the virus during the winter months. Fewer than one-third of frail elderly patients seroconvert following vaccination [15], implying that many such patients who are infected by influenza will also not develop a diagnostic rise in antibody titer. Community surveillance by the Scottish Centre for Infection and Environmental Health showed outbreaks of influenza A and B starting, respectively, in weeks 6 and 1 of 1995 [17]. The mortality curves for patients tended by vaccinated and unvaccinated HCWs appear to diverge several weeks before the first of these outbreaks.

The reduction in deaths seen in association with vaccination of HCWs appears to be greater than the observed effects on influenza-like illness or lower respiratory tract infection. Several factors may have contributed to this. Most influenza deaths are believed to be due to pneumonia, but the virus can cause encephalopathy, myocarditis, and myositis. Our results raise the possibility that a significant proportion of our patients may have died due to these clinically unrecognized complications. Alternatively, influenza may have had generalized effects (perhaps related to the massive production of interferon or other cytokines) that were not associated with classic respiratory symptoms. Communication disorders, such as dementia or dysphasia, are common in this patient group, and in these circumstances, accurate identification of clinical influenza or lower respiratory tract infection is often difficult. Many of the patients whom staff suspected of having viral illness or lower respiratory tract infection had vague symptoms or signs, and only a small number fulfilled our disease criteria. In addition, knowledge of patient and staff vaccination status may have influenced staff reporting of suspected viral illness and lower respiratory tract infection. Therefore, although it appears that vaccination of both HCWs and patients offered greatest protection against influenza-like illness, these morbidity data should be interpreted with caution.

Most cases of influenza-like illness in long-term care are due to other pathogens, such as coronavirus, RSV, rhinovirus, and adenovirus, all of which can cause pneumonia [5, 18]. We found evidence of RSV and adenovirus infection.

Table 3. Patient mortality, influenza-like illness, and lower respiratory tract infection: odds ratio (95% confidence interval) for the effects of vaccinating HCWs or patients against infleunza.

	Effect of vaccination of HCWs			Effect of vaccination of patients		
	Unvaccinated patients	Vaccinated patients	Unvaccinated and vaccinated patients	Unvaccinated HCWs	Vaccinated HCWs	Unvaccinated and vaccinated HCWs
Mortality	0.56 (0.34–0.94)	0.57 (0.35–0.91)	0.56 (0.40–0.80)	1.16 (0.75–1.79)	1.15 (0.64–2.06)	1.15 (0.81–1.64)
Deaths associated with pneumonia	0.64 (0.33–1.23)	0.56 (0.28–1.13)	0.60 (0.37–0.97)	0.87 (0.48–1.59)	0.75 (0.33–1.67)	0.83 (0.51–1.34)
Suspected viral illness	0.98 (0.65–1.48)	0.40 (0.26–0.62)	0.64 (0.48–0.87)	1.10 (0.75–1.62)	0.43 (0.27–0.69)	0.75 (0.56–1.02)
Influenza-like illness	0.86 (0.46–1.61)	0.24 (0.10–0.59)	0.57 (0.34–0.94)	0.68 (0.36–1.28)	0.20 (0.09–0.48)	0.47 (0.27–0.74)
Lower respiratory tract infection	0.77 (0.38–1.57)	0.59 (0.25–1.38)	0.69 (0.40–1.19)	0.74 (0.37–1.48)	0.57 (0.24–1.36)	0.67 (0.39–1.15)

Most authorities accept that influenza vaccination of elderly institutionalized patients is worthwhile, but many clinicians remain uncertain about the quality of the evidence for benefit [5]. A recent meta-analysis showed that vaccination of elderly institutionalized persons is associated with reduced risk of pneumonia or death [3]. However, in these studies, all patients were offered vaccine, and comparisons then were made between those who accepted and those who refused. This approach is likely to result in the unvaccinated control group consisting of patients who are more dependent and who have greater prevalence and severity of dementia [19]. Disability and dementia are associated with increased mortality, and therefore could act as confounding factors in the interpretation of the effects of vaccination. Case-control studies of deaths from influenza perhaps provide stronger evidence for benefit of influenza vaccine in frail elderly institutionalized persons [4]. However, the possibility of confounding factors still exists, including a tendency for physicians to more readily label death as due to influenza in unvaccinated frail elderly patients.

We had the opportunity to examine the effects of patient vaccination in a different study design, comparing hospital units with different vaccination policies. A policy of vaccination of patients was not associated with any significant beneficial effect on mortality rate, although there were fewer reported influenza-like illnesses. The low Barthel scores and high overall mortality rate reinforce how frail and dependent our long-term-care patients are. Barthel scores were slightly lower in the unvaccinated patient groups, but the absolute difference was small and not likely to be clinically significant. More importantly, it was not possible to randomly allocate patients to receive vaccination, given the established policies of the participating units. This may have introduced unsuspected bias between patient-vaccinated and patient-unvaccinated sites, which could differ in characteristics, thus affecting the study outcomes and masking the true effects of patient vaccination.

There is strong evidence from studies of various designs that influenza vaccine benefits community-dwelling elderly people. In a recent placebo-controlled double-blind trial, the incidences of both clinical and serologic influenza were reduced by ~50% [20]. Nonrandomized studies have shown that vaccination is associated with reductions in hospitalizations and deaths [21, 22]. Similar benefits with reductions in hospitalizations [23–25] and deaths [4] have been shown in case-control studies. There are several possible reasons why frail institutionalized elderly people may be less likely to benefit from influenza vaccination than healthy community-dwelling subjects. Many institutionalized elderly people have severe and debilitating chronic disease [6] in association with gross undernutrition [7]. Such persons are recognized to have impaired immune function and often do not develop adequate protective circulating antibody concentrations after influenza vaccination [8, 9].

In conclusion, we found that vaccination of HCWs against influenza was associated with reduced rates of mortality and influenza-like illness in geriatric medical long-term-care patients. These findings lend support to the recommendation of the CDC for vaccination of HCWs in contact with at-risk groups. It is possible that vaccination of HCWs may have additional benefits, in reducing their incidence of clinical influenza and thus decreasing work time lost due to illness. Vaccination of frail elderly long-term-care patients may not give clinically worthwhile benefits.

Acknowledgments

We thank the research nurses (Lesley Vass and Eileen McCaffrey), the HCWs who participated in this study, the occupational health nurses for coordinating vaccination of HCWs, Ian S. Symington of Glasgow Occupational Health for advice and support, the consultant geriatricians who allowed us to study their patients, and Medeva for donating influenza vaccine.

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