Immunogenicity of Inactivated Influenza Vaccine in Residential Homes for Elderly People

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Summary

One hundred and seventy residents of 11 Leicester City Council homes for the elderly, with a total of 515 beds, were studied during a 30-week period from September 1988 to March 1989 to determine the use of influenza vaccine, the levels of influenza antibody, the incidence of influenza, and the protection afforded by vaccination. The study group of 133 women and 37 men had a mean age of 85 years and 59% had one or more chronic medical conditions. The immunization rates by home for the 170 symptomatic residents ranged from 8% to 90% (mean 45%). Seventy-one sera, 36 from vaccinated and 35 from non-vaccinated residents were collected between 1 December 1988 and 24 March 1989 and were assayed for antibody to A/Taiwan/1/86 (H1N1), A Sichuan/2/87 (H3N2) and B/Beijing/1/87. Analysis revealed no statistically significant differences between the antibody profiles of vaccinated and unvaccinated subjects. Six influenza A and 6 influenza B infections were confirmed among the 170 subjects with upper respiratory tract infections. Influenza vaccination was not associated with significant levels of protection against influenza A or B. Studies of the haemagglutinins of the vaccine strains and influenza isolates during 1988/89 showed that they were closely related.

Introduction

Excesses of serious morbidity and death have consistently been demonstrated in elderly patients with certain chronic medical conditions during outbreaks of influenza [1–4]. Accordingly, the Department of Health, the Welsh Office, and the Scottish Home and Health Department suggest that annual influenza immunization be considered for elderly persons living in residential homes and long-stay hospitals, and for patients, especially the elderly, suffering with chronic pulmonary disease, chronic heart disease, chronic renal disease, diabetes and other less common endocrine disorders, and conditions involving immunosuppressive therapy [5]. Only 10%–20% of elderly and high-risk patients are, however, immunized each year [6, 7]; concern over vaccine safety, scepticism about vaccine efficacy, and the view that vaccination is unnecessary are the reasons cited most commonly [6, 8]. Often the efficacy of influenza vaccine has been determined by calculating the difference in the rate of illness between vaccinated and unvaccinated groups [9–12], but various respiratory viruses can masquerade as influenza during outbreaks [13], and so much of the available data on vaccine efficacy in the elderly may be misleading. During the 1988–9 influenza season, a year with a relatively low level of influenza activity nationally, we examined the use of influenza vaccine in 11 residential homes for elderly people in Leicester and studied the

incidence, aetiology, morbidity and mortality of acute upper respiratory tract viral infections in ambulatory patients [13]. The principal findings in the first report [13] were that lower respiratory tract complications developed during 45 (25%) of 179 upper respiratory tract episodes including 3 of 12 coronavirus infections, 3 of 9 respiratory syncytial virus infections, 2 of 4 adenovirus infections, 1 of 11 rhinovirus infections, but none of 5 influenza infections, the latter being identified by the complement fixation test. Respiratory infections were caused mostly by pathogens other than influenza during the influenza period documented nationally and the different viruses caused illnesses that were clinically indistinguishable. Thus there is considerable potential for influenza to be overdiagnosed by medical practitioners and patients and the efficacy of influenza vaccine could be underestimated accordingly. This second report concerns the levels of influenza antibody, as measured by single-radial haemolysis and haemagglutination inhibition assays, in vaccinated and non-vaccinated elderly residents, and the effectiveness of vaccine.

Subjects and Methods

Subjects: The 170 subjects enrolled in the study were residents of 11 Leicester City Council homes for the elderly who had symptoms of upper respiratory tract viral infection during the 30-week period including the week ending on 2 September 1988 (week 35) and the week ending on 24 March 1989 (week 12) inclusive. The homes had 482 'long-stay' beds, with an occupancy of approximately 95% by patients who may expect to remain there for the rest of their lives, and 33 'short-stay' beds occupied by temporary residents. Criteria for inclusion in the initial epidemiological study were symptoms lasting for at least 2 days and including two or more of nasal and throat symptoms, cough, lacrimation, or systemic features [13]. Patients with increasing dyspnoea, wheeze, severe cough, or productive cough for at least 2 days were deemed to have lower respiratory tract involvement. Details of the patients' medical, drug, and immunization histories for 1985 to 1988 were obtained from the medical practitioners and home wardens. Commercially available, split-product trivalent vaccine was administered on various dates during autumn 1988 by the patients' general medical practitioners. The vaccine contained 10 μg of A/Singapore/6/86 (H1N1), A/Sichuan/2/87 (H3N2), and B/Beijing/1/87.

The study: The 11 homes were telephoned twice weekly to establish the presence of upper respiratory tract infections. A 10 ml blood sample and nose and throat swabs were collected from symptomatic patients, and a convalescent serum sample was collected 3–4 weeks later. Acute or convalescent sera that were collected between 1 December 1988 (week 48) and 24 March 1989 (week 12) and were available in sufficient quantities after diagnostic serology in the parent study [13] were used to compare the influenza antibody levels of vaccinated and unvaccinated residents. Antibody to A/Taiwan/1/86 (H1N1), A/Sichuan/2/87 (H3N2), and B/Beijing/1/87 virus strains was measured either by haemagglutination inhibition (HI) tests after treatment of sera with receptor-destroying enzyme (RDE) to remove non-specific inhibitors or by single radial haemolysis (SRH).

Titres of < 10 in the HI test and zones < 2.5 mm in the SRH (i.e., negative results) were taken as 5 and 2, respectively, for calculations of the geometric mean titres (GMTs). When comparing the antibody levels of those vaccinated and those not vaccinated the geometric mean titre calculations excluded the titres of convalescent sera which confirmed a recent influenza infection. GMTs of both groups were calculated from $\log_{10}$ values of reciprocal titres, and comparison between the GMTs was made by Student's t test of log-transformed values. The significance of differences between proportions was computed by the χ^2 test.

Infection by influenza virus was diagnosed when there was a fourfold or greater increase in HI titre to influenza A/Taiwan/1/86 (H1N1) or A/Sichuan/2/87 (H3N2), or an increase of 3 mm or more in the single radial haemolysis assay for antibody to B/Beijing/1/87 virus. Protection against influenza was estimated by comparing the attack rates among vaccinated and non-vaccinated symptomatic residents. Differences between the infection rates were analysed by Fisher's exact probability test. To assess further the protection afforded by vaccination, the vaccination histories of patients with influenza A were compared with those of two controls per patient. The controls were matched for age (± 5 years), sex, the presence of chronic medical illness (matched for system affected), and residence in homes with influenza A.

The cross-reactivity between the vaccine strains, recent isolates, and isolates obtained during the winter of 1988/89 was assessed by means of HI tests with post-infection ferret sera. The ferret sera were treated with RDE before they were used in haemagglutination-inhibition tests.

Results

Demography and immunization rates: The demographic details of this population have been reported previously [13]. Briefly the study group comprised 133 women and 37 men with a mean age of 85.3 years (range 67–97); 59% had one or more chronic medical conditions. The immunization rates by home for the 170 symptomatic residents ranged from 8.3 to 90% (mean 45%). Between vaccinated and non-vaccinated residents there were no differences in sex or age or in presence of one or more chronic medical conditions.

HI titres and SRH diameters: Seventy-one sera—36 from vaccinated and 35 from non-vaccinated symptomatic residents—were collected at comparable time periods between 1 December 1988 and 24 March 1989 (Figure) and were available for HI and SRH tests. Analysis revealed no statistically significant differences between the antibody profiles of vaccinated and unvaccinated subjects. Reciprocal HI titres of less than 10 and/or SRH diameters of less than 2.5 mm, i.e. absence of antibody to A/Taiwan/1/86 (H1N1), A/Sichuan/2/87 (H3N2), and B/Beijing/1/87 were found in 66%, 47% and 8% of those vaccinated, respectively, and 76%, 72%, and 14% of those not vaccinated (Table I). Table I also shows that there were no statistical differences between the proportions of vaccinated and unvaccinated persons with reciprocal HI titres 40 or more and SRH zone diameters 4 mm or more, or between the geometric means of reciprocal HI titres to A/Taiwan/1/86 (H1N1), A/Sichuan/2/87 (H3N2), and B/Beijing/1/87.

Influenza vaccination and infection: Altogether 12 influenza infections were identified by HI serology. Six people in five homes developed symptoms of influenza B infection between 7 September 1988 (week 36) and 7 October 1988 (week 40); five people in three homes developed symptomatic illnesses with fourfold or greater rises in HI antibody to A/Sichuan/2/87 virus between 11 November 1988 (week 45) and 21 January 1989 (week 4); and one person developed a symptomatic illness with fourfold or greater rises in HI antibody to A/Taiwan/1/86 virus on 22 December 1988 (week 51).

Protection against influenza was estimated by comparing the attack rates among vaccinated and non-vaccinated symptomatic residents. Despite the low antibody titres the attack rate for influenza A and B among symptomatic individuals was only 7% (12 per 170 subjects) in the 11 homes. Influenza vaccination was not associated with statistically significant levels of protection—among the 163 people with known immunization status there were three symptomatic cases of influenza A and B among 73

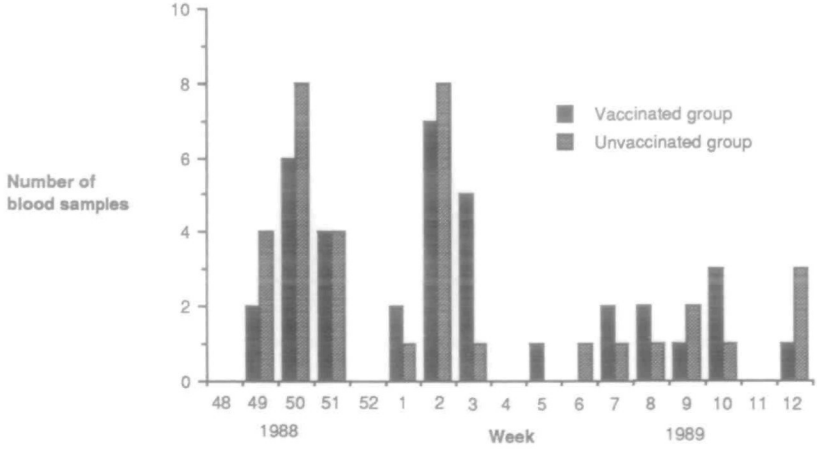

Figure. Distribution by date of collection of blood samples from vaccinated and unvaccinated patients.

Table I. Number and percentage of vaccinated and unvaccinated elderly persons with reciprocal HI titres < 10 and ≥ 40, SRH zone diameters < 2.5 mm and > 4 mm, and geometric mean reciprocal HI titres and SRH zone diameters

	No. (%) with reciprocal HI titre < 10 and/or SRH diameter < 2.5 mm		No. (%) with reciprocal HI titre ≥ 40 and/or SRH diameter > 4 mm		Geometric mean reciprocal HI titre [and SRH zone diameter]	
Antigen	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated
A/Taiwan/86	23/35* (66)	26/34 (76)	8/35 (23)	6/34 (18)	10.0	8.3
A/Sichuan/87	16/34 (47)	23/32 (72)	13/34 (38)	8/32 (25)	18.8	10.7
B/Beijing/87	3/36 (8)	5/35 (14)	33/36 (92)	30/35 (86)	[7.7]	[7.0]

*Numerator/denominator; $p > 0.05$ for all χ^2 analyses which compare vaccinated and unvaccinated groups; $p > 0.05$ for both Student's t tests which compare log-transformed reciprocal antibody titres and zone diameters of vaccinated and unvaccinated subjects.

vaccinated (attack rate = 4.1%) and nine among 90 non-vaccinated subjects (attack rate = 10%) ($p = 0.25$). For all 11 homes, i.e. homes with and without influenza, there was one case of influenza A among 73 vaccinated (attack rate = 1.4%) and five cases of influenza A among 90 non-vaccinated subjects (attack rate = 5.5% ($p = 0.32$). For the four homes with influenza A, there was one case among 16 vaccinated (attack rate = 6.2%) and five among 36 non-vaccinated residents (attack rate = 13.9%) ($p = 0.78$). Similarly for the five homes with influenza B infection there were two cases among 47 vaccinated (attack rate = 4.2%) and four among 41 non-vaccinated residents (attack rate = 9.7%) ($p = 0.55$).

Only one of the six patients with influenza A had received vaccine in 1988. Review of the immunization status of 12 age-, sex, and illness-matched controls in homes with influenza A infection (who had upper respiratory tract infections other than influenza) revealed that only 2 of 12 were vaccinated during autumn 1988, i.e. the immunization rates of matched residents with and without influenza were identical.

Influenza vaccine and cross-reactions with isolates circulating during 1988/9: The haemagglutinin antigens of the H1N1 and H3N2 vaccine strains were compared with those of A/Chile/1/83 H1N1 and A/Leningrad/360/86 H3N2 and their natural variants, including variants that were isolated during winter 1988–9, by means of HI tests with post-infection ferret sera (Tables II and III). Three hundred and thirty-one isolates were typed by the Virus Reference Laboratory during winter 1988–9 [14]. Most (238) were A/Taiwan/1/86 H1N1 variants and the HI tests in Table II show that the A/Singapore/6/86 vaccine virus strain was closely related to the prevalent strain. Similarly, the A/Sichuan/2/87 H3N2 vaccine virus strain also resembled the A/England/427/88 H3N2 variant that was isolated during the winter (Table III).

Discussion

This study highlights the low antibody titres of elderly residential persons to influenza strains prevalent in 1988–9 and indicates that they were little improved by immunization, notably during the period when influenza A infections were prevalent in England and Wales [14]. In mammalian species there is a decline in immune function that begins at the time of sexual maturation and progresses throughout life [15]. Antibody responses decline with ageing [16, 17], and the response of elderly people to influenza vaccine tends to be lower than in younger individuals [12, 18], especially when

Table II. Cross-reactions of A/Singapore/6/86 H1N1 with A/Chile/1/83 and its natural variants in HI tests

	Haemagglutination-inhibition titres using post-infection ferret sera against:			
	A/Chile/83	A/Swit/85	A/Sing/86	A/Taiwan/86
A/Chile/1/83	**640**	320	< 40	< 40
A/Switzerland/79/85	320	**640**	< 40	< 40
A/Singapore/6/86[a]	< 40	80	**640**	640
A/Taiwan/1/86[b]	40	80	640	**5120**

Note: a = vaccine strain, b = prevailing H1N1 strain during winter 1988–9.

Table III. Cross-reactions of A/Sichuan/2/87 H3N2 with A/Leningrad/360/86 and its natural variants in HI tests

	Haemagglutination-inhibition titres using post-infection ferret sera against:				
	A/Len/86	A/Guan/87	A/Sich/87	A/Syd/87	A/Eng/88
A/Leningrad/360/86	**640**	40	< 40	80	80
A/Guandong/9/87	160	**160**	40	160	160
A/Sichuan/2/87[a]	80	320	**640**	640	640
A/Sydney/1/87	40	80	160	**640**	640
A/England/427/88[b]	160	160	320	640	**2560**

Note: a = vaccine strain, b = prevailing H3N2 strain during winter 1988–9.

there are concurrent medical conditions such as malignancy or cardiovascular disease [17, 19]. The period between collection of pre- and post-vaccination sera in most studies of vaccination of elderly people has usually been several weeks [20], and, since as many as one-half of all those vaccinated do not achieve HI titres greater than 40 [12] and the HI antibody response may be of brief duration [21, 22], it is perhaps not surprising that the elderly residential patients in Leicester had such low HI titres despite vaccination. Despite the low titres the attack rate for influenza A and B only reached 4.1% in vaccinated and 10% in non-vaccinated symptomatic residents, and, although the incidence was more than twice as high in those not vaccinated, that difference is not statistically significant. A small outbreak of influenza B occurred between 7 September 1988 (week 36) and 7 October 1988 (week 40), a period when medical practitioners are generally embarking upon their programme of vaccination, and when patients are at risk of infection. However, vaccination was not associated with a reduced attack rate for influenza when influenza B infections were discounted from the calculations of efficacy.

The factors associated with outbreaks of influenza are not clearly understood. Susceptibility to influenza virus infection is considered to be inversely related to the titre of serum HI antibody and a serum HI titre of approximately 30–40 represents a 50% protective level of antibody against infection by homologous virus [23]. Whereas high HI titres are generally protective, universally low titres such as those observed in the current study do not necessarily

herald severe outbreaks, even when influenza is introduced into homes for the elderly.

Previous studies of influenza-like illness in nursing homes suggest a protective efficacy of only 27% against influenza type A and 21% against type B [12], but vaccination has been found to reduce the incidence of pneumonia, hospitalizations and deaths by 60–70% [24]. This is not a universal finding [25], however, and was not demonstrated in the current study. Our study, which was based on 170 symptomatic individuals in homes with 515 beds, illustrates how unrewarding influenza vaccination of elderly residential people can be during non-epidemic years. The trend towards protection in this study is in keeping with similar trends in previous studies in homes for the elderly, and, until the failure of vaccination is established by large well designed prospective studies, we believe that vaccine delivery to current target groups should be improved and that the search for better influenza vaccines should continue.

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