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Influenza A among community-dwelling elderly persons in Leicestershire during winter 1993–4; cigarette smoking as a risk factor and the efficacy of influenza vaccination

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SUMMARY

In a prospective study of community-dwelling people 60–90 years of age, we examined the coverage of influenza vaccine during 1992–3 and 1993–4, the efficacy of vaccination in reducing serologically-confirmed clinical episodes of influenza A during 1993, and the effect of cigarette smoking. During 1992 and 1993, influenza vaccine was given to 106/215 (49%) and 120/204 (59%) people with risk conditions, and 84/225 (37%) and 103/235 (44%) without risk conditions. Influenza vaccination and general practitioner consultations during 1992 were independent predictors of vaccination in 1993, but current smoking was a negative predictor. Of 209 unimmunized people, 8/35 (23%) smokers had clinical influenza as compared with 11/174 (6%) non-smokers (OR 4·4, 95% CI 1·6 to 11·9). Of 371 non-smokers, 1/197 (0·5%) vaccinees had influenza as compared with 11/174 (6%) non-vaccinees (OR 0·075, 95% CI 0·587 to 0·009). No cases of influenza occurred among 21 current smokers who were vaccinated.

INTRODUCTION

Influenza and its complications account for 5000–30000 deaths annually in England and Wales with more than 80% of deaths occurring in people aged $\geqslant$ 75 years [1–3]. In the United Kingdom annual influenza immunization has for many years been strongly recommended for 'high-risk' adults and children; i.e. for those with certain chronic medical conditions (pulmonary disease including asthma, heart disease, renal disease, diabetes mellitus), immunosuppression due to disease or treatment, and those living in long stay residential accommodation where rapid spread may follow the introduction of infection. Historically, these recommendations evolved from the increase in morbidity and mortality from influenza among 'high risk' people, and trials in healthy young adults, which established the efficacy of vaccine to be about 70–90% when there is a good match between vaccine and circulating virus strains [4, 5]. They did not originate from placebo-controlled studies in the elderly or 'high-risk' groups, so influenza vaccine recommendations differ from country to country [6]. Because the costs and benefits of an age-related policy of immunization for the United Kingdom have been unclear, the United Kingdom has been one of a few countries without such a policy.

Recent cohort and case-control studies in Canada, the United States and United Kingdom have shown conclusively that influenza vaccination of the elderly reduces hospital admissions for pneumonia and influenza, influenzal deaths and deaths from all causes [7–15]. However, few studies assessed the benefits of vaccination among elderly people while differentiating subjects by risk status, and none further stratified patients by age; most considered only those aged $>$ 65 years. Moreover, many of the studies on the

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effectiveness of influenza immunization have been carried out in North America where the cost of vaccine and cost and pattern of health care differ from those in the United Kingdom.

Data from the United Kingdom, which confirm that the elderly without high risk conditions are at risk from the serious complications of influenza, have been examined in cost-benefit analyses. These focused on costs per life-year gained and reveal that annual influenza immunization is not only medically justified for all those $\geqslant 75$ years but also represents good value for money in comparison with other health care interventions [16]. However, to justify a further change in policy, say, to include all those aged $\geqslant 65$ years, further information is required on the burden of influenza in the United Kingdom with respect to hospitalization and medical consultations, and the reductions that can be expected from the use of vaccine in the elderly.

During 1991–2 we studied immunization against influenza among people aged $\geqslant 60$ years living at home in Leicestershire [17]. We extended the study during 1992–3 and 1993–4 to include an assessment of the impact of respiratory viral infections [18, 19]. The present report focuses on vaccine coverage and targeting; it describes the predictors of immunization, and examines the relation of immunization status and cigarette smoking to the incidence of serologically-confirmed clinical influenza A during 1993–4.

METHODS

Population and study

The study was conducted among people $\geqslant 60$ years during the winters of 1992–3 and 1993–4 in Leicestershire. During April–June 1992 we sent letters to 800 of the 129000 people aged $\geqslant 60$ who lived in Leicestershire inviting them or their spouse, or both, to participate in the study. The sample was randomly selected by the family health services authority computer. Patients living in residential care were excluded. Basic demographic data, and medical and drug history were collected at recruitment. During surveillance periods each subject was contacted weekly by telephone at a prearranged time. Using a questionnaire each volunteer was asked whether an acute upper respiratory tract infection had occurred during the previous week and whether any new medication or vaccine had been administered. When illness was reported, a record was made of date of onset and the presence or absence of rhinorrhoea; thick nasal discharge; nasal stuffiness; sneezing, sore throat, hoarseness, 'gritty' or watery eyes; neck-, face-, head- or earache; myalgia; dry cough; productive cough; sweating; rigors; feverishness; breathlessness at rest; wheeze; and pain or discomfort on breathing. We also ascertained the extent of incapacitation, and whether a doctor had been consulted, drugs had been prescribed, and the patient had been admitted to hospital.

Symptomatic subjects were seen at home as soon as possible after the onset of symptoms. Diagnostic specimens were collected as described previously [18], and symptoms were converted into syndromes based on published criteria [18–20]. The illness was considered lower respiratory if symptoms of productive cough, wheezy breathing, or pain on respiration were present, irrespective of other respiratory symptoms.

We enrolled 533 volunteers in total, 441 during the first winter and 439 during the second [17]. Surveillance for upper respiratory tract infections during the second winter began during week 35 of 1993. Altogether 427 volunteers were studied throughout the period of influenza A activity which occurred during weeks 42–50 inclusive of 1993. The 207 men and 220 women were aged 63–89 (median 72 years; mean 72·9, S.D. 5·6) and 60–90 (median 70 years; mean 71·6, S.D. 6·1) years respectively upon recruitment. More men than women [164 (79%) *vs.* 97 (44%), χ^2 test, $P < 0{\cdot}001$] had a history of smoking, but men and women were comparable with respect to the Department of Health's designated 'high risk' medical conditions for influenza vaccination (195, 46%); age $\geqslant 75$ years (128, 30%), hospitalization during the preceding 5 years (177, 41%); attendance at a hospital outpatient department during the preceding 12 months (182, 43%); consultation with their medical practitioner during the preceding 12 months (371, 87%); and vaccination against influenza in 1993 (119, 51%). The project was approved by the Leicestershire ethics committee and signed informed consent was obtained from all volunteers.

Laboratory studies

Paired acute and convalescent serum samples were stored at $-20\,^{\circ}C$ and tested later by complement fixation tests for antibodies to influenza A and B. Haemagglutination inhibition tests were also carried out to identify infections caused by influenza subtype A (H3N2) that were close antigenically to the

A/Beijing/32/92 variant included in the 1993/94 vaccine. A fourfold rise in antibody was taken as indicating infection.

Statistical analysis

Simple regression and multiple logistic regression were used to identify factors associated with vaccination against influenza during the 1993 immunization season. Forward stepwise multiple logistic regression was used to estimate the probability of vaccination by calculating adjusted odds ratios for potentially important explanatory variables.

RESULTS

Epidemiology of vaccination

Overall 190 of 440 (43%) subjects were vaccinated during 1992 (vaccination status of one subject missing) and 223 of 439 (51%) subjects were immunized during 1993 (χ^2 5·116, $P < 0·01$). Table 1 shows that 84 of 225 (37%) without the Department of Health's designated 'high risk' medical conditions were vaccinated during 1992, and 103 of 235 (44%) were vaccinated during 1993. Although there were increasing levels of immunization with increasing numbers of 'high risk' medical conditions during both 1992 and 1993 (1992, χ^2 for trend = 8·19, $P < 0·01$; 1993, χ^2 for trend = 12·65, $P < 0·001$), only 106 of 215 (49%) people with risk conditions were immunized during 1992, and 120 of 204 (59%) were immunized during 1993.

Factors associated with immunization

Using simple regression analysis, the following factors were significantly ($P < 0·05$) associated with a higher immunization rate in 1993: the number of high risk medical conditions (mean, 0·6 per person in vaccinees; 0·4 per person in non-vaccinees), vaccination during 1992 (67% among vaccinees; 14% among non-vaccinees), the number of medical consultations per annum (median, 3 for vaccinees; 2 for non-vaccinees), hospitalization during the preceding 5 years (mean 0·8 admissions among vaccinees; 0·6 among non-vaccinees), cardiovascular disease (45% among vaccinees; 31% among non-vaccinees), diabetes (5% among vaccinees; 1% among non-vaccinees), and presence of one or more high risk conditions (73% among vaccinees; 61% among non-vaccinees). Current smoking (9·5% among vaccinees; 17% among non-vaccinees) was significantly associated with a lower immunization rate in 1993. The following factors were not associated with higher or lower immunization rates: having never smoked (36% among vaccinees; 41% among non-vaccinees), age (median 71 years among vaccinees; 70 years among non-vaccinees), sex (50% male among vaccinees; 46% male among non-vaccinees), medication for chronic pulmonary disease (13% among vaccinees; 9% among non-vaccinees), immunosuppression (1% among vaccinees; 0·5% among non-vaccinees), and visits to a hospital outpatient department (mean, 1·4/person among vaccinees; 1·3/person among non-vaccinees).

The factors that were most strongly associated with immunization in elderly subjects during 1993 were analysed further using multiple logistic regression. Two models were developed, one incorporating a history of immunization against influenza in 1992, and the second excluding it. The analysis showed that the estimated probability of influenza vaccination in 1993 in those who were immunized in 1992 was increased by 71% in comparison with the remainder [adjusted odds ratio 1·71 (95% CI interval 1·56–1·87)]. It was increased independently by 9% [adjusted odds ratio 1·09 (1·002–1·195)] in those who visited their general practitioner 3 or more times per annum in comparison with the remainder. Forward stepwise regression selected only 2 variables into the model excluding prior immunization. The estimated probability of influenza vaccination in 1993 increased by 16% in those who visited their general practitioner 3 or more times per annum in comparison with the remainder [adjusted odds ratio 1·16 (95% CI 1·06–1·28)]. The estimated probability of vaccination was decreased independently by 13% [adjusted odds ratio 0·87 (0·76–0·99)] in those who were current smokers in comparison with the former smokers and non-smokers.

Vaccine efficacy

A total of 427 subjects were surveyed weekly throughout an outbreak of influenza which caused symptomatic influenza in 20 subjects from 18 October 1993–19 December 1993. Seventeen influenza A infections occurred as single infections, 1 occurred in association with a rhinovirus and 2 in association with coronavirus infections. Nineteen clinical influenza A infections occurred in 209 non-vaccinees (one patient was vaccinated 4 weeks after onset of influenza and

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Table 1. *Number* (*percentage*) *of people immunized during 1992 and 1993 who had no illness for which vaccine is indicated, and one, two, and three illnesses for which vaccine is recommended*

Year	No vaccine indication vaccinated/total (%)	One vaccine indication vaccinated/total (%)	Two vaccine indications vaccinated/total (%)	Three vaccine indications vaccinated/total (%)	Total vaccinated/total (%)
1992	84/225 (37)	87/184 (47)	18/29 (62)	1/2	190/440 (43)
1993	103/235 (44)	101/178 (57)	17/24 (71)	2/2	223/439 (51)

Table 2. *Number* (*percentage*) *of people with influenza A during 1993 who were either vaccinees or non-vaccinees and current smokers or non-smokers*

Infection status	Vaccinees		Non-vaccinees		Total (%)
	Smoker (%)	Non-smoker (%)	Smoker (%)	Non-smoker (%)	
Influenza	0	1 (0·5)	8 (23)	11* (6)	20 (5)
No influenza	21	196 (99·5)	27 (77)	163 (94)	407 (95)
Total	21	197	35	174	427

* One subject received vaccine one month after influenza A and is therefore considered to be a non-vaccinee.

for comparative analyses was not considered a vaccinee), and 1 case occurred among 218 vaccinees (Table 2). Thirteen (65%) of the 20 cases occurred in people without 'high-risk' medical conditions. Eight (23%) cases of clinical influenza occurred among 35 smokers who were not vaccinated, and 11 (6%) occurred among 174 non-smokers who were not vaccinated [crude odds ratio 4·4 (95% CI interval 1·6–11·9)]. The crude odds ratio for protection against laboratory confirmed clinical influenza afforded by vaccine in non-smokers as compared with non-smokers who were not vaccinated was 0·075 (95% CI 0·587–0·009), which gives an estimated vaccine efficacy of 92·5% (95% CI 41·3–99·1%).

Burden of influenza

The median duration of symptoms of influenza A was 17·5 days (range 6–71 days); it was not significantly different in smokers compared to non-smokers nor in those with and without high-risk medical conditions. Five of 7 (71%) people with medical indications for vaccine developed lower respiratory illness as compared with 10 of 13 (77%) without high-risk conditions (NS). Altogether 9 (45%) patients saw their general practitioner; all were prescribed antibiotics; 5 received domiciliary consultations; the mean number of consultations per case was 0·75 (range 1–6); 12 cases were confined to bed for a median of 2 days (range 0–8 days); 15 (75%) were unable to cope with routine domestic activities, and one person with chronic airways disease was hospitalized for 6 days.

DISCUSSION

The influenza outbreak in 1993–4 provided the opportunity to study the efficacy of influenza vaccine in non-residential elderly people and the effect of cigarette smoking upon natural infection with influenza A. By studying vaccine distribution in the elderly during 1993 and 1994 we also examined adherence to the Department of Health recommendation to vaccinate selectively individuals most at risk of serious illness or death.

Influenza vaccination of non-residential at-risk elderly people increased from 42·5% in 1991–2 [17], to 49% in 1992–3, and 59% in 1993–4. Although this reflects an annual growth of between 15–20%, and coverage increased with an increase in number of high risk conditions, our subjects were volunteers in a longitudinal study of respiratory viral infections and are likely to be more health conscious than the general population and have higher immunization levels. Indeed, among groups of 25000–35000 patients registered with practices in England and Wales participating in the General Practitioners Research Database, 38% of high-risk 65–74 year olds were immunized during 1991–2, rising to 44% during

1993–4, and 40% high risk people aged ⩾ 75 years were immunized during 1991–2, rising to 44% during 1993–4 [21]. Despite the improved distribution over time these data show that a substantial proportion of elderly at risk people were not being immunized despite annual recommendations from the Chief Medical Officer being sent to all general practitioners.

Simple and multiple logistic regression were used to identify predictors of vaccination. Multiple logistic regression analysis showed that the estimated probability of vaccination in 1993 in people immunized during 1992 was increased by 71% (95% CI 56–87%) in comparison with the remainder. As judged by the acceptance of vaccine in successive years influenza vaccine is evidently well tolerated. Altogether 125 of 147 (85%) people who were vaccinated during 1992 and studied in 1993 were re-immunized. Similarly 239 of 275 (87%) people immunized in Leicestershire during 1988–9, 1989–90, or 1990–1 were vaccinated the following year [17].

Influenza vaccine was targeted poorly. The annual number of visits to the surgery was more strongly associated with vaccination than the presence of 'high risk' medical conditions, and almost as many elderly people (44%) without high risk conditions were immunized in 1993 as those with one high risk condition (57%). Indeed coverage in the elderly with lung disease (52%) was similar to the level in those without risk conditions. The reasons for poor targeting is unclear but the arrangement whereby practitioners purchase vaccine and can dispense it to all-comers to recoup their outlay may be a contributory factor.

As in an earlier study in the United States [22], we showed that current smoking is a negative predictor of immunization. This is of concern since acute lower respiratory complications of 'non-influenzal upper respiratory tract infections' and rhinovirus infections are more frequent in current smokers [18, 23], and morbidity of influenza in smokers, as assessed by lost work days and confinement to bed, is greater than in non-smokers [24]. Moreover, current smokers have higher rates of asymptomatic [25] and symptomatic influenza than non-smokers. In this study the unadjusted odds ratio for clinical influenza A in current smokers was 4·39 (95% CI 1·6–11·9) in comparison to non-smokers. Similarly, in the studies by Kark and colleagues [24, 26] the odds ratio for clinical influenza among young male smokers during an outbreak in a military unit was 2·42 (95% CI, 1·53–3·83) and the risk ratio among female military recruits who smoked was 1·44 (95% CI 1·03–2·01) in comparison to non-smokers. The proportion of clinical influenza attributable to smoking has been estimated at 13% in female recruits [26], 31% in young men [24], but was 72% in the current study of the elderly.

The attack rate of 9% for symptomatic influenza A among non-vaccinated subjects in our study was identical to the rate among elderly placebo-recipients in a double-blind study of influenza vaccine during 1991–2 in the Netherlands [27]. In the Dutch study, influenza vaccine had an efficacy of 61% (95% CI 32–78%) in preventing serologically-confirmed influenza A. In our study, the efficacy of influenza vaccine in preventing serologically-confirmed clinical influenza in non-smokers was 92% (95% CI 41–99%). There were no cases of influenza among 21 vaccinees who were current smokers, but 8 cases occurred among 35 smokers who were not vaccinated, indicating that influenza vaccine is as effective in smokers as non-smokers.

Our study, together with the recent cohort and case control studies [7–15], the placebo-controlled study [27], and meta analyses of past studies [28, 29], provide overwhelming evidence that influenza vaccine prevents clinical influenza, complications and death in the elderly. Our observations that 65% of clinical cases of influenza in this study occurred in elderly people without 'high risk' medical conditions; the median duration of illness was 17·5 days; 75% had lower respiratory illness and restriction of domestic activities; 60% were confined to bed; and that 45% were reviewed by a doctor and prescribed antibiotics indicate that 'uncomplicated' influenza in the elderly, both in those with and without high-risk conditions, is not trivial and that vaccination of the over 65's is medically justified. Our data and those of Irish and colleagues [21] indicate that the risk-disease based programme achieved poor coverage. Conceivably a policy of immunization of the over 65's with central purchasing of vaccine and payment related to coverage might lead to better health care of all elderly people, reduce winter admissions, and represent good value for money in comparison with other health care interventions.

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