Epidemiol. Infect. (2002), **129**, 515–524. © 2002 Cambridge University Press
DOI: 10.1017/S095026880200780X Printed in the United Kingdom

Comparison between cohorts vaccinated and unvaccinated against influenza and pneumococcal infection

B. CHRISTENSON* AND P. LUNDBERGH

Department of Communicable Disease Control and Prevention, Karolinska Hospital, Stockholm, Sweden

(*Accepted 11 August 2002*)

SUMMARY

This study characterizes possible confounders that might make cohorts vaccinated and unvaccinated against influenza and pneumococcal infection different at baseline, with the hypothesis that the two cohorts are comparable. The similarity between health and demographic data was analysed by a randomized, multivariant study addressed to 10 000 persons aged 65 years and older in Stockholm County and was carried out in the form of a postal inquiry during the period December 2000 to May 2001. The study-population response rate was 78%. Of these, 66% (5120 persons) had been given at least one influenza vaccination during the 3-year study period (1998–2000), 50% (3780) had received one pneumococcal vaccination and 78% had received both vaccines during the period. The vaccination rate was lower in the age group 65–69 years (60%), compared with elderly cohorts aged over 70 years (67–72%, $P<0{\cdot}001$). Elderly persons living in nursing homes or institutions had higher vaccination rates than persons living in their own households (72 *vs.* 67%). Persons with underlying chronic diseases had higher vaccination rates (71%, $P<0{\cdot}001$) than those without underlying chronic diseases. Vaccine recipients had fewer days in hospital, compared with non-recipients. Unvaccinated persons with myocardial disease had nine times more days in hospital than vaccinated persons with myocardial disease. Vaccination against pneumococcal infection had an additional effect with influenza vaccination in reducing hospitalization for chronic lung diseases; influenza vaccination alone did not have this effect. In conclusion, the influenza and pneumococcal-vaccine recipients were older and had significantly more chronic lung and heart conditions than the unvaccinated cohort.

INTRODUCTION

Influenza and pneumonia have been shown to be the fifth leading cause of death among persons aged 65 years and older in the United States [1–3]. There is no reason to believe that the situation is otherwise in Sweden or worldwide. The risks of complications, hospitalization and death from influenza and pneumonia are greater among persons aged 65 years and older and for persons with underlying disease conditions [4]. In Sweden, with a population of approximately nine million, 900–4600 deaths per year could be related to excessive mortality during the influenza seasons in the period 1993–8 [5]. However, influenza and pneumococcal vaccines have been little used in many countries. In Sweden, only 4–8% of all persons received influenza vaccination between 1990 and 1995, and 2000 persons were given pneumococcal vaccinations yearly. In the United States, the vaccination cover of elderly persons is regarded as unsatisfactory, in spite of the fact that about 65 and 45% are vaccinated against influenza and pneumococcal infection,

* Author for correspondence.

respectively [6]. Previously, in Sweden, the recommendation for influenza and pneumococcal vaccination concerned only persons with chronic respiratory and heart diseases. New recommendations for pneumococcal and influenza vaccination were issued by the Swedish National Board of Health and Welfare in 1994 and 1997, respectively. Pneumococcal and influenza vaccination should be considered for all persons aged 65 years and older. Doubts concerning the benefit of immunization with these vaccines have contributed to the under use of these vaccines. Prospective studies concerning the efficacy of the 23-valent, pneumococcal polysaccharide vaccine have not been convincing [2, 7–11]. However, clinical and epidemiological trials have found pneumococcal vaccination to be efficacious in preventing pneumonia in older people [12, 13] and there have been retrospective cohort studies that have shown that pneumococcal vaccination of elderly persons with chronic lung disease is associated with reduced hospital admissions for pneumonia [14, 15]. A recent study demonstrated the additive benefit of influenza and pneumococcal vaccination in elderly persons with chronic lung disease [16]. The benefit of annual influenza vaccination has been documented in several case-control and retrospective cohort studies [17–21]. Is efficacy has been confirmed, especially during epidemic years, when there is a close match between the circulating virus and the vaccine strain [22]. We have previously reported in a large-scale, prospective study on the efficacy of influenza and 23-valent pneumococcal vaccination in preventing hospital admissions and death in adults aged 65 years or older in Stockholm County. We showed that there was a significant reduction of hospitalization for influenza and pneumococcus-related diseases and a reduction of mortality from all causes in the vaccinated cohort [23]. An important issue was whether the vaccinated and unvaccinated cohorts were comparable at baseline. We theorized that the vaccination rates for elderly people with heart and lung diseases were higher than for those without these conditions, as prior recommendations had concerned only individuals with these conditions. The benefits of the vaccinations would then be further enhanced. In the present study, we compared the health and demographic data in cohorts vaccinated and unvaccinated against influenza and pneumococcal infections aged 65 years and older. We also compared the number of days in hospital care in the vaccinated and unvaccinated cohorts.

METHODS

Background

The effectiveness of influenza and pneumococcal vaccination in preventing hospitalization and death was investigated during a 3-year prospective study (1998–2000) of all individuals aged 65 years and older (260 000) in Stockholm County [23]. Approximately 120 000 persons (40 %) of the target population had been given a yearly influenza vaccination and a total of 79 000 had received pneumococcal immunization during the 3-year study period. Data from the study showed a significant reduction of hospitalization for influenza and pneumococcus-related diseases and of deaths from all causes. An important issue was whether the vaccinated and unvaccinated cohorts were similar. This study characterized possible confounders that might make vaccinated and unvaccinated cohorts different at baseline.

Study population

The study was performed in Stockholm County which had a population of 1 823 210 on 1 January 2001. The subjects were selected on a statistical basis from the Stockholm County Council Population Register and were considered to be representative of the population in these age cohorts. The selection was addressed to 9999 individuals aged 65 years and older, registered in the County. The investigation was carried out in the form of a postal inquiry during the period December 2000 to March 2001. Two postal reminders were sent out. A selection of 300 persons was then contacted by telephone. A total of 7836 persons (78 %; 59 % women and 41 % men) replied to the questionnaire concerning health and demographic data and stated whether they had been given one or more influenza immunizations and/or a pneumococcal immunization. Of the 7836 responders in the study, 26 % were aged between 65 and 69 years, 25 % between 70 and 74 years, 22 % between 75 and 79 years, and 27 % were 80 years old or older. The study participants completed questionnaires on general background characteristics, including medical condition, whether they had been feeling well or ill, marital and household status, education, physical activity and smoking habits. The questions also concerned their reasons for being vaccinated and their arguments for refraining from vaccination. For analyses, we matched the vaccination data with discharge diagnoses, according to the International Classification of Diseases, tenth revision (ICD-10-CM), from

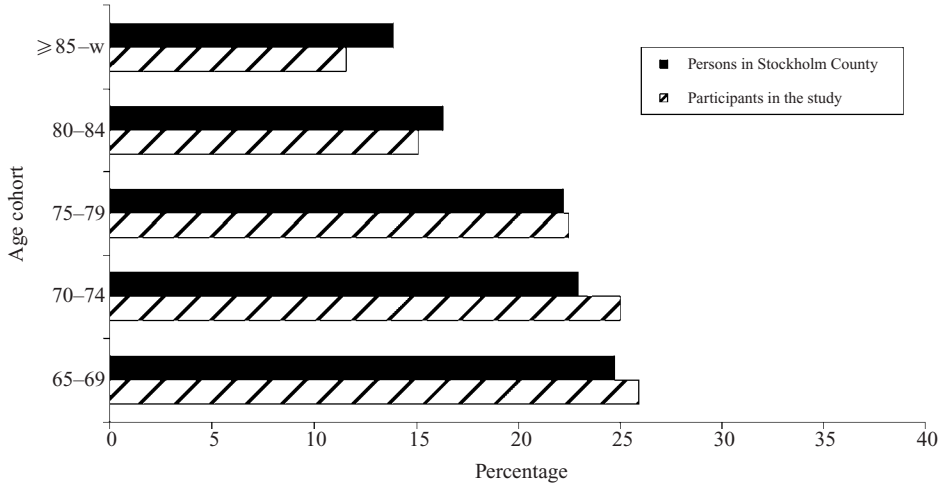

Fig. 1. Age distribution of study population and the corresponding age cohorts in Stockholm County.

all the hospitals in Stockholm County. Data were obtained from the administrative database of Stockholm County Council for the persons included in the study concerning days in hospital care for endpoint diagnoses. Estimates of factors besides vaccination that could have influenced the number of days in hospital were analysed.

Drop-out

A certain drop-out occurs in all surveys by questionnaires. It can be divided into two categories, object drop-out, when the entire questionnaire is missing, and internal drop-out, when the answer to a single question is missing. The internal drop-out was low for all the questions in the survey. Two questions, one in which the respondent was asked to state his or her highest educational qualification and the other concerning vaccination against pneumococci, had an internal drop-out of 3%. The question about education was perceived by many to be a sensitive one, which may explain the drop-out. However, the internal drop-out for these questions was small and therefore it is unlikely that it distorted the results. The object drop-out, which amounted to 20%, may also be distorted in certain respects. Probably many residents in institutions did not take part in the inquiry, which was confirmed by the telephone calls which we received in the course of the investigation.

Statistical analysis

Statistical analyses were performed, using the confidence interval for a proportion and the χ^2 test for categorical variables. Also, the binomial distribution and the z-test were used for comparison of two proportions. Odds ratios and 95% confidence intervals were calculated for the association between influenza and pneumococcus-related medical conditions in vaccinated cohorts, compared with unvaccinated. Poisson regression analysis was used to estimate the association of influenza and pneumococcal vaccination and the factors which influence the number of days of hospital treatment for influenza and pneumococcus-related diagnosis.

RESULTS

The age distribution of the study population, compared with the total age distribution in these age cohorts in Stockholm County, is shown in Figure 1. Of those who responded to the inquiry, 59% were women and 41% men, which is in accordance with the age distribution between men and women in these age cohorts in Stockholm County (40·2% men and 59·8% women). Women predominated in the oldest age group with 14%, compared with 8% for the men. This is due to the fact that there are more women than men in the oldest age cohort. In the two youngest age groups, the men predominated.

A total of 66% (5120 persons) of the responders had at least one influenza vaccination between 1998 and 2000, 3572 persons (46%) in 1998, 4002 persons (51%) in 1999 and 4196 (54%) in 2000. Fifty-five percent had had an influenza vaccination in each of the 3 years and 78% had also been given a pneumococcal vaccination. Younger age cohorts, between 65 and 69 years, had significantly fewer vaccinations

https://doi.org/10.1017/S095026880200780X Published online by Cambridge University Press

Table 1. *Cohorts vaccinated and unvaccinated against influenza and pneumococcal infection, calculated as percentages of each age group*

	Influenza			Pneumococcal		
Ages (years)	Vaccinated* (%)	Unvaccinated (%)	95% CI (±)	Vaccinated (%)	Unvaccinated (%)	95% CI (±)
	[*n* = 5120 (66)]	[*n* = 2511 (33)]	1·05	[*n* = 3780 (50)]	[*n* = 3539 (47)]	
65–69	1188 (60)	808 (40)	2·15	913 (47)	1040 (53)	2·21
70–74	1292 (67)	628 (33)	2·10	1017 (54)	858 (46)	2·26
75–79	1238 (72)	481 (28)	2·12	929 (57)	707 (43)	2·40
80–84	808 (71)	333 (29)	2·64	575 (54)	499 (46)	2·98
⩾85	594 (69)	261 (31)	3·09	346 (44)	435 (56)	3·48

* At least once between 1998 and 2000.
CI, confidence interval.

Table 2. *Baseline characteristics of study cohort. Percentage of each category*

	Influenza			Pneumococcal		
	n	Vaccinated (%)	95% CI (±)	*n*	Vaccinated (%)	95% CI (±)
Study cohort	7631	66		7319	50	
Male	3123	41		3020	41	
Female	4508	59		4299	59	
Marital status						
Married or living with partner	4121	70	1·40	4035	55	1·54
Widowed or living alone	3394	64	1·62	3215	47	1·73
Household						
Own household	7110	67	1·09	6858	52	1·18
Nursing home or institution	427	72	4·27	377	42	4·98
Education						
Elementary school	3637	63	1·57	3472	48	1·66
Junior secondary school	1435	70	2·37	1378	55	2·62
Upper secondary school	996	71	2·82	964	56	3·13
University/College	1318	74	2·37	1277	57	2·72
Current smoking	973	59	3·09	953	45	3·16

(60%, $P < 0{\cdot}001$), compared with the elderly age groups, in which between 67 and 72% were vaccinated against influenza (Table 1).

Half of the elderly had been given a pneumococcal vaccination during the same period; 47% had refused a pneumococcal vaccination and 4% could not remember whether they had been given one or not. The youngest age group (65–69 years) and the oldest (85 years and older) had lower, pneumococcal vaccination rates compared with the other age groups. Most pneumococcal vaccinees had also received an influenza vaccination (99%), whereas a negligible number of the vaccinees had received only a pneumococcal vaccination (31 persons).

The baseline characteristics of the study population are given in Table 2. Demographic data showed that a 94% of the responders lived in their own households and 6% were living in nursing homes or institutions. Persons living in nursing homes and institutions were vaccinated against influenza to a greater extent (71%, $P < 0{\cdot}001$) than persons with their own households (67%), while the opposite was the case for pneumococcal vaccination (42 *vs.* 52%). Many residents in institutions did not take part in the inquiry, which may have affected the results, insofar as certain categories tended to be underestimated.

A total of 55% of the study population were married or living with a partner. Of these, 70% had been

https://doi.org/10.1017/S095026880200780X Published online by Cambridge University Press

Table 3. *Self-perceived state of health in the last 12 months*

	Influenza			Pneumococcal		
How they felt	*n*	Vaccinated (%)	95% CI (±)	*n*	Vaccinated (%)	95% CI (±)
Very well	1813	60	2·25	1770	47	2·33
Fairly well	3499	69	1·53	3374	55	1·68
Neither well nor ill	1208	69	2·62	1138	51	2·90
Ill	798	69	3·21	742	49	3·60
Very ill	155	65	7·50	149	48	8·02

Table 4. *Characteristics of physical conditions*

	Influenza			Pneumococcal		
	n	Vaccinated (%)	95% CI (±)	*n*	Vaccinated (%)	95% CI (±)
Able to take a short walk	6863	67	1·11	6620	52	1·20
Can climb stairs	5291	65	1·29	5123	51	1·37
Can get on a bus or train	5836	66	1·22	5648	53	1·30

given at least one influenza vaccination and 55% a pneumococcal vaccination. For persons living alone, these figures were 64 and 47%, respectively.

The education level was a predictive factor for vaccination. Persons with little education were vaccinated to a lesser extent against both influenza and pneumococcal infection than persons with higher education ($P<0{\cdot}001$).

A total of 13% of the responders smoked daily. Older persons smoked less than younger ones. The proportion of smokers was higher in the unvaccinated influenza group, compared with the vaccinated (16 *vs*. 11%). Among those who smoked, the majority (59%) were vaccinated against influenza, whereas the pneumococcal-vaccination rate was lower among smokers (45%).

One question concerned the self-perceived state of health in the last 12 months (Table 3). A majority of the responders who had felt fairly well in the last 12 months were vaccinated ($P<0{\cdot}001$). These applied for both influenza and pneumococcal vaccinations. Persons who felt very well were vaccinated against influenza to a lesser extent than those who felt fairly well, neither well nor ill, or very ill.

The characteristics of the self-reported, physical conditions is shown in Table 4. More than 90% of the responders could take a short walk. Men (93%) declared to a greater extent than women (90%) that they could manage to walk. No difference between those vaccinated and unvaccinated against influenza was found in those able to take a short walk, whereas more persons who had received a pneumococcal vaccination were able to walk. Fever persons vaccinated against influenza could climb stairs or get on a bus or train, compared with the unvaccinated. There was no difference between pneumococcal-vaccinated and unvaccinated persons as regarded climbing stairs, whereas more vaccinated persons were able to get on a bus or train. The reasons for not being able to climb stairs or get on a bus or train were heart problems (27%), having to use a walking frame (23%) and lung problems (15%). The most common answer was other, unspecified reasons.

Table 5 shows the self reported, medical conditions as percentages of the cohorts. The tendency to be influenza and pneumococcal-vaccinated was significantly greater ($P<0{\cdot}001$) among individuals who suffered from any of the chronic diseases mentioned. Among those who suffered from chronic lung disease and/or myocardial disease 79% were vaccinated against influenza and 63 and 61%, respectively, were vaccinated against pneumococcal infection.

Reasons for not receiving vaccination

A total of 32% of the study population were not vaccinated in any of the given years. Figure 2 gives the reasons for not being vaccinated. 'Other reasons' was the most common answer; these were medical reasons, such as rheumatism, the waiting time at the

https://doi.org/10.1017/S095026880200780X Published online by Cambridge University Press

Table 5. *Self-reported medical condition*

	Influenza				Pneumococcal			
Diagnoses	Vaccinated ($n=5120$) (%)	Unvaccin. ($n=2511$) (%)	OR (CI)*	$P<$	Vaccinated ($n=3780$) (%)	Unvaccin. ($n=3536$) (%)	OR (CI)*	$P<$
Chronic disease (at least one)	55·4	45·3	1·5 (1·4–1·7)	0·001	56·2	47·6	1·4 (1·3–1·6)	0·001
Chronic lung disease	9·2	4·6	2·1 (1·6–2·7)	0·001	9·7	5·6	1·8 (1·4–2·3)	0·001
Myocardial disease	17·4	10·2	2·1 (1·7–2·5)	0·001	17·6	11·5	1·7 (1·4–2·0)	0·001
High blood pressure	58·2	30·3	1·3 (1·2–1·5)	0·001	37·3	31·6	1·3 (1·2–1·4)	0·001
Diabetes	15·3	11·5	1·4 (1·2–1·7)	0·001	15·2	12·5	1·3 (1·1–1·5)	0·001
Other chronic diseases	23·1	21·5	1·4 (1·2–1·6)	0·001	31·7	18·8	1·4 (1·2–1·6)	0·001

* OR, odds ratio; CI, confidence interval.

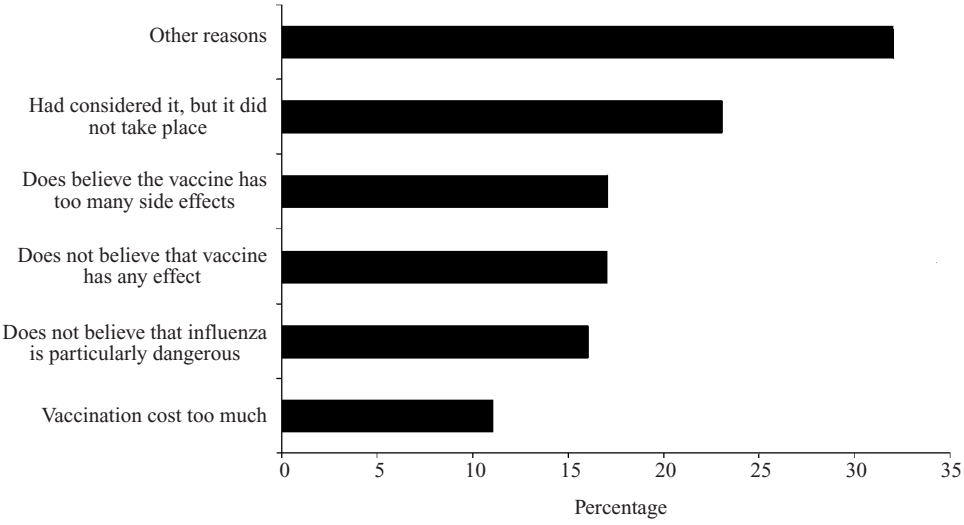

Fig. 2. Reasons for not receiving vaccination.

medical centre, and relatives and friends who had become ill after vaccination. The least often stated reason for refraining from vaccination was the cost of being vaccinated, in spite of the fact that the cost of influenza and pneumococcal vaccinations is not reimbursed in Sweden.

Factors that influenced the number of days in hospital

The majority of the responders (91%) had not been admitted to hospital. Of the responders, 388 (4%) had been admitted to hospital for myocardial diseases which resulted in 4549 days in hospital, an average of 12 days per person. Both influenza- and pneumococcal-vaccinated recipients with chronic heart failure had fewer days in hospital, compared with unvaccinated persons with heart diseases. Unvaccinated persons with myocardial diseases had nine times more days in hospital than vaccinated persons with myocardial diseases. Pneumococcal vaccination led to fewer days in hospital for persons with chronic lung disease, compared with unvaccinated persons with chronic lung disease. All vaccinated persons with chronic diseases had significantly fewer days of hospital care (46%), compared with unvaccinated persons with chronic diseases. The interactions between different factors and vaccination against influenza are summarized in Table 6. A cross (+) indicates that persons in this group had fewer days in hospital care whether they were vaccinated or unvaccinated. It can be seen

https://doi.org/10.1017/S095026880200780X Published online by Cambridge University Press

Table 6. *Factors that, together with vaccination influenced the number of days in hospital* (+ *indicates fewer days of hospital care* $P<0{\cdot}05$)

Factors	Vaccinated	Unvaccinated
Smoking	+	
Chronic heart disease	+	
Chronic disease	+	
Felt very well	+	
Felt quite well	+	
Felt indifferently well	+	
Felt ill		+
Felt very ill	+	
Elementary school (Felt quite well)	+	
Junior secondary school (Felt quite well)	+	
Upper secondary school (Felt quite well)	+	
University/College (Felt quite well)		+

that persons who smoked daily and who were vaccinated had fewer days in hospital than those who smoked daily and were unvaccinated.

An estimated model (Fig. 3) was compiled to show the interaction between vaccination and other factors that could influence the number of days in care for influenza and pneumococcus-related diseases. It must be stressed that most persons who were pneumococcal-vaccinated also had influenza immunization (99%). The self-perceived state of health in the model included those who had felt very well, fairly well and neither well nor ill. Individuals who smoked daily and were vaccinated had significantly fewer days in hospital, compared with persons who smoked and were unvaccinated. Also non-smokers who were vaccinated had fewer days in hospital than unvaccinated non-smokers. All baseline factors are included in the model, besides sex, marital status, being able to get on a bus or train, high blood pressure and diabetes. This indicates that all factors besides these influenced the number of days in hospital for vaccinated persons compared with unvaccinated. Age alone did not interact with vaccination against influenza or pneumococcal infection as regarded days in care.

Analysis of drop-out

The oldest age cohort had a lower response frequency than the younger ones. This was due to the high proportion of persons of this age living in institutions. Sixty-eight percent responded in the oldest age group, compared with the highest response rate of 83% in the 65–69 years age group. A comparison within each age group showed that women between 80 and 84 years responded to a lesser extent than men (76 *vs.* 81%). Otherwise, there were no statistical differences in the responses to the inquiry between the sexes in the different age groups.

DISCUSSION

This study was designed to evaluate the hypothesis that cohorts vaccinated and unvaccinated against influenza and pneumococcal infections were comparable. The similarity of the health and demographic data for these cohorts was analysed using a sample of our previous, large-scale, prospective study of all individuals aged 65 years and older in Stockholm County [23]. The total response frequency was nearly 80%, which must be considered high. The willingness to participate in surveys in Sweden has decreased in recent years. One reason is that the number of surveys and the amount of telemarketing have increased. In spite of this, 68% of the persons in the oldest age cohort responded.

The object drop-out, which amounted to about 20%, may be distorted in certain respects. Really old persons usually have a lower response frequency than younger ones, because a high proportion of persons of this age live in institutions. Residents in institutions probably took part in the inquiry to a lesser extent. We consider that this may have affected the results of the investigation, insofar as certain categories tended to be underestimated – those who had been vaccinated and those who were in a poor state of health. The demographic data showed that residents living in nursing homes and institutions had a higher vaccination rate (72%) than persons living in their own households (62%), which is in conformity with the finding that high-risk persons have a higher vaccination rate than low-risk persons [17]. It was also shown that fewer persons vaccinated against influenza could climb stairs or get on a bus which might indicate that they were in poorer condition than the unvaccinated.

Data from our previous influenza and pneumococcal vaccination study of the elderly indicated a significant reduction of hospital admissions in the vaccinated cohort, compared with the unvaccinated cohort, for influenza and pneumococcus-related diseases, and an overall reduction of deaths from all causes in the vaccinated cohort [23]. The most important issue was to

https://doi.org/10.1017/S095026880200780X Published online by Cambridge University Press

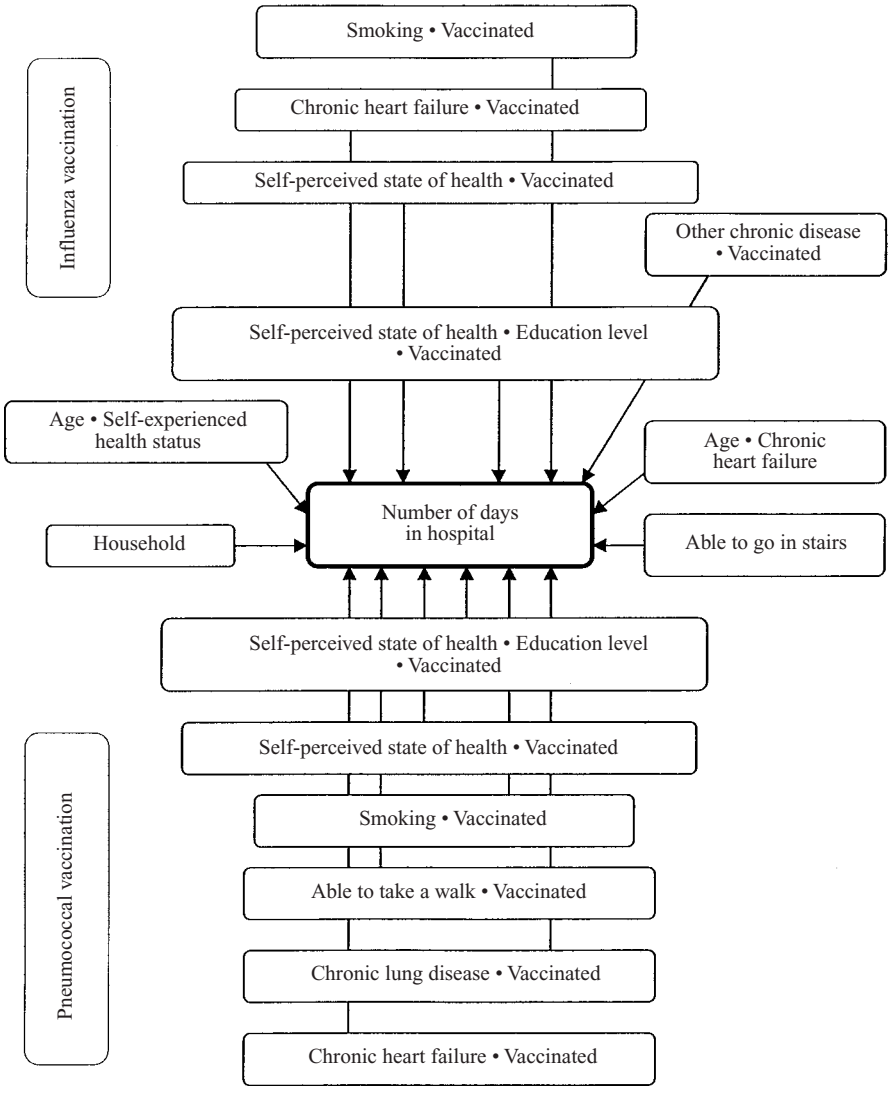

Fig. 3. Estimated model for factors that, together with vaccination, influenced the number of days in hospital.

find out whether the vaccinated and unvaccinated cohorts were comparable. It was important to exclude the probability that our findings were partly due to the fact that the vaccinated cohort was healthier or younger than the unvaccinated cohort. Previous recommendations in Sweden for influenza and pneumococcal vaccinations have mainly concerned persons with heart failure and chronic lung diseases. This favoured the assumption that high-risk persons, those with chronic lung and heart diseases, were more disposed to receive influenza and pneumococcal immunization [24]. We theorized that the vaccination rate for elderly persons with underlying heart and/or lung diseases was higher than that for elderly persons without these conditions. If this was the case, the benefit of the vaccinations would be further enhanced.

The study supported the assumption that those with chronic lung and heart diseases had a higher vaccination rate than those without these conditions [21, 25]. Most persons in the study who received a pneumococcal vaccination had also had an influenza immunization, whereas very few persons had only a pneumococcal immunization. It is assumed that the two vaccines interact with each other and contribute to the overall protective effect [16]. The estimated model (Fig. 3) illustrated that other factors besides vaccination influenced the number of days in hospital for influenza and pneumococcus-associated diseases. It should be pointed out that it is far from obvious what formal statistical tests mean and how the results of model estimates should be interpreted. Any doubts and contradictions in the results from the model should be accepted as part of the results. Attempting

https://doi.org/10.1017/S095026880200780X Published online by Cambridge University Press

to get round problems by trying afterwards to adjust and refine the model will lead to increased difficulties in evaluating the results. An appropriate interpretation of our findings confirmed our previous result that influenza and pneumococcal vaccination reduced hospitalization for influenza and pneumococcus-associated diseases. Both influenza- and pneumococcal-vaccinated recipients with chronic heart disease had fewer days in hospital, compared with unvaccinated individuals with this condition. As regarded chronic lung disease, the effect in reducing the number of days in hospital could be found only in recipients who had received pneumococcal vaccination. As 99% of the pneumococcal vaccine recipients had also received an influenza immunization it was difficult to decide whether this effect was additive or an effect of the pneumococcal vaccine alone [16]. It was also demonstrated that smokers and self-perceived state of health, together with vaccination, reduced the number of days in hospital, compared with unvaccinated smokers with the same, self-perceived state of health. Vaccinated individuals with chronic diseases had fewer days in hospital than unvaccinated individuals with chronic diseases.

In conclusion we found higher vaccination rates in elderly age cohorts and in those living in nursing homes and institutions. The vaccinated cohort had a significantly higher frequency of chronic lung and myocardial diseases, as well as other chronic diseases, than the unvaccinated cohort. Vaccinated persons with chronic lung and heart disease had a reduced number of days of hospital care, compared with unvaccinated persons with the same diseases. Our findings supported previous findings about the beneficial effect of the influenza and pneumococcal vaccinations.

REFERENCES

1. Centers for Disease Control and Prevention. Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1998; **47** (RR-6).
2. Centers for Disease Control and Prevention. Prevention of pneumococcal disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1997; **46** (RR-8): 1–24.
3. Nicholson KG, Wiselka MJ, May A. Influenza vaccination of the elderly: perceptions and policies of general practitioners and outcome of the 1985–86 immunization program in Trent, UK. Vaccine 1987; **5**: 302–6.
4. Goavert ME, Thijs CTMCN, Sprenger MJW, Dinant GJ, Knottnerus JA. The efficacy of influenza vaccination in elderly individuals: a randomized double-blind placebo-controlled trial. JAMA 1994; **272**: 1661–5.
5. Linde A. Influensarapport 30/6 – Summary of influenza seasons and number of deaths. Swedish Institute for Infectious Disease Control, 1999.
6. Centers for Disease Control and Prevention. Pneumococcal and influenza vaccination levels among adults aged <65 years – United States. MMWR 1998; **47**: 797–802.
7. Forrester HL, Jahnigen DW, LaForce FM. Inefficacy of pneumococcal vaccine in a high-risk population. Am J Med 1987; **83**: 425–30.
8. Fedson DS. Pneumococcal vaccination in the prevention of community-acquired pneumonia: an optimistic view of cost-effectiveness. Semin Respir Infect 1993; **8**: 285–93.
9. Fedson DS, Musher DM. Pneumococcal vaccine. In Plotkin SA, Mortimer EA Jr, eds. Vaccines, 2nd ed. Philadelphia, PA: WB Saunders Co, 1994: 517–64.
10. Simberkoff MS. Pneumococcal vaccination in the prevention of community-acquired pneumonia: a skeptical view of cost-effectiveness. Semin Respir Infect 1994; **8**: 294–9.
11. Örtqvist Å, Hedlund J, Burman LA, et al. Randomized trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people. Lancet 1998; **351**: 399–403.
12. Fine MJ, Smith MA, Carson CA, et al. Efficacy of pneumococcal vaccination in adults. A meta-analysis of randomized controlled trials. Arch Intern Med 1994; **154**: 2666–77.
13. Sisk JE, Moskowitz AJ, Whang W, et al. Cost-effectiveness of vaccination against pneumococcal bacteremia among elderly people. JAMA 1997; **278**: 1333–9.
14. Nichol KL, Baken L, Vuorenma J, Nelson A. The health and economic benefits associated with pneumococcal vaccination of elderly persons with chronic lung disease. Arch Intern Med 1999; **159**: 2437–42.
15. Koivula I, Sten M, Leunonen M, Mäkelä PH. Clinical efficacy of pneumococcal vaccine in the elderly: a randomized, single-blind population-based trial. Am J Med 1997; **103**: 281–90.
16. Nichol KL. The additive benefits of influenza and pneumococcal vaccinations during influenza seasons among elderly persons with chronic lung disease. Vaccine 1999; **17**: S91–93.
17. Foster DA, Talsma AN, Furumotot-Dawson A, et al. Influenza vaccine effectiveness in preventing hospitalization for pneumonia in the elderly. Am J Epidemiol 1992; **136**: 296–307.
18. Fedson DS, Wajda A, Nicol JP, Hammond GW, Kaiser DL, Roos LL. Clinical effectiveness of influenza vaccination in Manitoba. JAMA 1993; **270**: 1956–61.
19. Mullooly JP, Bennett MD, Hornbrook MC, Barker WH, Williams WW, Patriarca PA, Rhodes PH. Influenza vaccination programs for elderly persons: cost-effectiveness in a health maintenance organization. Ann Intern Med 1994; **121**: 947–52.
20. Nichol KL, Margolis KL, Wuorenma J, von Sternberg T. The efficacy and cost effectiveness of vaccinations

against influenza among elderly persons living in the community. N Engl J Med 1994; **331**: 778–84.
21. Nichol KL, Wuorenma J, von Sternberg T. Benefits of influenza vaccination of low-, intermediate-, and high-risk senior citizens. Arch Intern Med 1998; **158**: 1769–76.
22. Ahmed AH, Nicholson KG, Nguyen-Van Tham JS, Pearson JCG. Effectiveness of influenza vaccine in reducing hospital admissions during the 1989–90 epidemic. Epidemiol Infect 1997; **118**: 27–33.
23. Christenson B, Lundbergh P, Hedlund J, Örtqvist Å. Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in adults aged 65 years or older: a prospective study. Lancet 2001; **357**: 1008–11.
24. Höglund D, Stenqvist K. Influenza vaccination coverage among the elderly in the Göteborg area. Läkartidningen 2001; **98**: 156–8.
25. Gross PA, Hermogenes AW, Sacks HS, Lau J, Lewandowski RA. The efficacy of influenza vaccine in elderly persons: a meta-analysis of the literature. Ann Intern Med 1995; **123**: 518–27.