Epidemiol. Infect. (2001), **126**, 261–268. Printed in the United Kingdom

Prognostic factors for influenza-associated hospitalization and death during an epidemic

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(*Accepted 29 November 2000*)

SUMMARY

To predict which patients with current high-risk disease in the community may benefit most from additional preventive or therapeutic measures for influenza, we determined prognostic factors for influenza-associated hospitalization and death in a general practice-based case-control study among this segment of the vaccine target population with high influenza vaccination rates. In 103 general practices followed during the 1996/7 influenza epidemic, cases were either hospitalized or died due to influenza, bronchitis, pneumonia, diabetes, heart failure or myocardial infarction. Age- and gender-matched controls were randomly sampled from the remaining cohort. Information was collected by review of patient records. In total, 119 cases and 196 matched controls were included. Of the cases, 34, 25 and 4% were hospitalized for acute pulmonary and cardiac disease and diabetes, respectively, and 37% died. Multivariate conditional logistic regression analysis revealed that presence of chronic obstructive pulmonary disease, heart failure, previous hospitalization, high GP visiting rate and polypharmacy were independent prognostic factors. Several non-modifiable determinants can be used to ensure targeting additional preventive or therapeutic measures at the most vulnerable segment of the vaccine target group.

INTRODUCTION

Influenza continues to cause considerable morbidity and is considered one of the world's major killer diseases [1, 2]. Recently, much attention has been given to a potentially upcoming influenza pandemic that may result in large numbers of casualties, especially among those with high-risk medical conditions [3]. To reduce the health and economical burden of influenza infection, use of inactivated vaccines by vulnerable patient groups is a major topic in preventive health care policy [4]. However, although influenza vaccination rates are reaching high levels, immunization does not confer full protection [5, 6].

In order to increase the impact of additional clinical measures against influenza or its sequelae such as the use of neuraminidase inhibitors or pneumococcal vaccines, knowledge about patients who are most vulnerable from complications of influenza is indispensable. Physicians should be able to routinely reach patients at highest risk, even if immunized against influenza, to direct other preventive or therapeutic regimens [7]. Additional studies with the

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primary objective to assess clinical determinants of an increased risk of serious influenza-associated complications among the largest segment of the vaccine target group, outpatients with current high-risk medical conditions, are therefore needed.

As part of an ongoing study to assess the effectiveness of a nation-wide collaborative primary care programme to enhance influenza vaccine uptake in the Netherlands [8], we conducted a case-control study to establish prognostic indicators for influenza-associated hospitalization and death among adult patients with high-risk chronic disease given current immunization rates.

METHODS

Our study is part of an evaluation of the nationwide intervention programme 'Tailor-made prevention' that was implemented between 1995 and 1997 to foster population-based prevention of influenza and cervical cancer in Dutch general practice [8, 9]. A sample of 56 computerized general practice (GP) centres using the GP information system ELIAS (SMS Cendata, Wageningen) involving 103 GPs, participated in the present study. ELIAS has been developed to support large-scale epidemiological studies in primary care by facilities such as integration of coded information on disease status, reasons for encounter and medical prescriptions in the computerized patient records, and search modules to enable storage of data in a study database [10]. Participating GP centres were spread all over the Netherlands and relevant anonymous data were supplied by GPs to the data-management centre of the Julius Center, University Medical Center Utrecht.

We designed a case-control study nested in the centres' cohort of adult outpatients with high-risk chronic medical conditions requiring annual influenza vaccination according to Dutch immunization guidelines [11]. In October 1996, patients with potential current high-risk disease who were eligible for inclusion into our study were selected by means of a computerized influenza prevention software module. Details on the module's stepwise selection procedures have been described elsewhere [7]. In short, patients were identified using their date of birth and presence of medical disorders was identified on the basis of relevant entries of ICPC diagnosis codes, ATC medical drug codes and tags indicating chronic disease in computerized patient records. Conditions were grouped as pulmonary disease (chronic obstructive pulmonary disease [COPD], asthma, lung cancer or other pulmonary disease), heart disease (heart failure, myocardial infarction, valvular heart disease, angina, and cardiomyopathy), diabetes mellitus, renal disease and other diseases (including malignant disorders, neurological disease). In November 1996, we identified a cohort of 18163 patients with registered codes indicating potential high-risk disease among the total vaccine target population including healthy elderly (n = 32425 persons).

Identification of hospitalized and fatal cases during 1996/7 influenza epidemic

The epidemic period was defined from 23 December 1996 to 16 February 1997 as influenza peak activity was observed between these dates [12]. Questionnaires were sent fortnightly to participating GPs to identify hospitalized or deceased patients. Study subjects qualified as a case if they were admitted to the hospital during the epidemic with a primary diagnosis of an acute episode of influenza, bronchitis, exacerbation of underlying lung disease, pneumonia, diabetes dysregulation, congestive heart failure or myocardial infarction or if they died from these causes. After the epidemic the case definition was verified by the participating GPs. If a specialist certification letter was present at the GP's office, a photocopy was obtained.

Our objective was to establish prognostic factors among the segment of the adult vaccine target outpatient population with current high-risk disease, regardless of age. To ensure the presence of current high-risk disease at inception of the cohort in November 1996, potential cases had to be excluded from the study population if no registration of GP contact for their chronic condition in the preceding 24 months was present (so-called 'inactive patients') or if they moved out of the general practice or died before the epidemic ('ghost patients'). Verification of current disease and specific diagnosis at baseline until the beginning of the epidemic was made retrospectively by the GPs in April 1997. Surveillance of complications during the epidemic resulted in 202 potential cases identified and screened for eligibility. We excluded 37 patients without chronic medical conditions at baseline or lack of GP contact before the epidemic and 46 patients because no eligible controls (i.e. with current high-risk disease) were available for

Table 1. *Characteristics of cases* ($n = 119$) *and controls* ($n = 196$)

	Cases		Controls	
Characteristic*	No.	%	No.	%
Age $\geqslant$ 65 years	83	70	120	61
Male	64	54	111	56
NHS insurance	103	87	133	68
Medical history				
Asthma/other PD	3	2	13	6
COPD	24	20	30	15
CHF	9	8	7	4
Myocardial Infarction	7	6	17	9
Other CVD	14	12	62	32
Diabetes	12	10	28	14
Other HD	—	—	4	2
$\geqslant$ 1 high-risk disease	50	42	35	18
GP visits				
1–2	26	22	78	40
3–4	20	17	50	25
$\geqslant$ 5	73	61	68	35
Previous hospitalization	36	30	19	10
No. drugs (mean, SD)	2·8	1·5	3·5	1·5
Vaccine uptake				
1994	72	61	109	56
1995	81	68	127	65
1996	105	88	174	89

* PD, pulmonary disease (tuberculosis, pleurisy, lung cancer); COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; CVD, cardiovascular disease (angina pectoris, chronic ischaemic disease, atrial fibrillation, stroke, paroxysmal tachycardia, cor pulmonalis, valvular heart disase, pulmonary embolism); HD, high-risk disease (renal dysfunction, leukemia, multiple sclerosis, hyperthyreoidy); GP, general practitioner; SD, standard deviation.

these patients. In all, 119 cases were available for analysis.

Identification of controls

In April 1997, using a computerized sampling schedule, we randomly sampled three control patients for every potential case from the database with the remainder of the cohort, matched for age (in the same 5-years age-category) and sex. Controls were not reported as hospitalized or deceased during the epidemic. Of the 357 controls that were sampled from the database for the 119 remaining cases, 12 were excluded because no data were available for these patients. In addition, 149 patients without high-risk disease at baseline, with a lack of GP contacts or who moved out or died before the epidemic were excluded, because they, retrospectively, were not part of the cohort, which resulted in 196 valid controls.

Measurements in cases and controls

Baseline demographic information on age, gender and health insurance (private or National Health Service) was collected by data generated using the influenza prevention module [7]. Further detailed information on potential risk factors was collected retrospectively by review of GP medical records. Presence of concomitant high-risk disease and previous hospitalization resulting from complications related to the high-risk conditions in the 12 months preceding the epidemic was verified by GPs. Use of medical drugs was reported if used chronically for the conditions and the number of GP consultations during the preceding year was counted. Immunization of both cases and controls who complied with the written invitation took place during mass vaccination sessions at the GP's office in November 1996. In The Netherlands, most outpatients receive the vaccine through the GP immunization programme [8]. The trivalent subunit vaccine composition complied with WHO recommendations and matched well with circulating strains [12]. A person was taken to be a vaccinee for 1996 if the ICPC-code R44.1 (required for reimbursement), was present in the patient record within 2 months prior to the start of the epidemic [7].

Statistical analysis

Data entry and univariate analysis were performed with use of the commercially available statistical package SPSS for Windows (version 9.0). Distributions of all variables by case and control status were calculated using descriptive statistics. Univariate analysis included t-tests for continuous variables and χ^2 tests for categorical variables to assess statistically significant differences between cases and controls. Multivariable conditional logistic regression analysis for matched case-control studies with EGRET (Statistics and Epidemiology Research Corporation, Seattle, Washington) was applied to assess independent associations of potential prognostic indicators with the outcome parameter. In the modelling procedure, only those variables were entered in the multivariable model that were associated with the outcome at a P-level less than 0·20 in the univariate

https://doi.org/10.1017/S0950268801005180 Published online by Cambridge University Press

Table 2. *Prognostic factors for influenza-related hospitalization and death: total study population and specialist-confirmed cases and controls are given*

	Total study population ($n = 315$)			Confirmed cases and controls ($n = 129$)		
Characteristic	Cases ($n = 119$) No. (%)	Controls ($n = 196$) No. (%)	Adjusted OR (95% CI)	Cases ($n = 49$) No. (%)	Controls ($n = 80$) No. (%)	Adjusted OR (95% CI)
NHS insurance*	103 (87)	133 (68)	3·7 (1·5–8·7)	42 (86)	55 (69)	3·0 (0·6–13·6)
COPD†	24 (20)	30 (15)	3·5 (1·5–8·3)	9 (18)	13 (16)	5·0 (1·1–23·7)
CHF†	9 (8)	7 (4)	3·3 (1·0–11·2)	5 (10)	4 (5)	9·9 (1·3–73·4)
> 1 high-risk disease‡	50 (42)	35 (18)	3·2 (1·5–7·2)	23 (47)	13 (16)	5·6 (1·5–21·1)
⩾ 5 GP consultations¶	73 (61)	68 (35)	2·5 (1·3–4·8)	31 (63)	29 (36)	4·1 (1·2–13·9)
Previous hospitalization§	36 (30)	19 (10)	1·9 (0·9–4·1)	10 (20)	7 (9)	1·0 (0·3–4·1)
No. drugs (x, S.D.)	2·8 (1·5)	3·5 (1·5)	1·3 (1·1–1·7)	3·4 (1·4)	2·1 (1·4)	1·4 (1·0–1·9)
Vaccinated in 1996‖	105 (88)	174 (89)	0·8 (0·4–2·0)	41 (84)	73 (91)	0·9 (0·2–4·6)

* Versus private insurance.
† Versus other high-risk disease.
‡ Versus one high-risk disease.
¶ Versus 1–4 GP consultations.
§ Versus no hospitalization.
‖ Versus no vaccination in 1996.

analysis (eight variables in total). Missing data on an independent variable were considered as absence of the factor. Both stepwise and backward elimination procedures were used to construct the final model. Influenza vaccine status was forced into the final model to assess its potential protectiveness irrespective of statistical significance. As under-use of vaccines is most common in younger populations [13], we specifically addressed the relative influence of potential prognostic factors in subgroups of high-risk patients over and under 65 years of age. In a subgroup analysis in age-strata (< 65, ⩾ 65 years), the same variables of the overall final model were forced into both separate models. Robustness of the models was assessed by the Hosmer–Lemeshow goodness-of-fit test. Adjusted odds ratios (OR) and their 95% confidence intervals (CI) were calculated. Vaccine effectiveness was calculated as 1 minus the odds ratio (as approximation of the relative risk) in vaccinees times 100%.

RESULTS

Mean age of the patient cohort of 18163 persons was 62 years (SD 18, range 18–102 years) and 49% were male. Based on coded entries, cardiovascular and pulmonary disease appeared present in 36 and 32%, respectively, whereas 18% were registered with various codes indicating more than one high-risk condition. Diabetes, renal disease and immune-related disease appeared far less frequent: 12, 1 and 1%, respectively.

Of the 119 incident cases, 44 (37%) cases had died, 31 (26%) suffered from an exacerbation of underlying pulmonary disease, 22 (18%) from heart failure, 8 (7%) from pneumonia, 8 (7%) from myocardial infarction, 5 (4%) from diabetes dysregulation and in 1 the only diagnosis was influenza. Written certification of case diagnosis by a specialist was obtained in 49 (41% of cases). Mean hospital stay was 13 days (95% CI 10–17 days) and appeared equal in those under and over 65 years. Sixteen (16%) were treated at the intensive care unit. Mean age of cases and controls was 70 years (S.D. 14 years) and 55% were male. The baseline characteristics of cases and controls are summarized in Table 1.

In multivariate analysis, the following factors appeared to be independently associated with the outcome in the total study population (Table 2): previous hospitalization (odds ratio [OR] 1·9; 95% CI 0·9–4·1), ⩾ 5 GP consultations in the preceding year (OR 2·5; 95% CI 1·3–4·8), polypharmacy (OR 1·3; 95% CI 1·1–1·7 per additional drug), presence of COPD (OR 3·5; 95% CI 1·5–8·3), heart failure (OR 3·3; 95% CI 1·0–11·2) or more than one high-risk condition (OR 3·2; 95% CI 1·5–7·2) and NHS insurance (OR 3·7; 95% CI 1·5–8·7). Influenza vaccination in 1996 had a moderate and statistically non-significant protective effect only (20% reduction

https://doi.org/10.1017/S0950268801005180 Published online by Cambridge University Press

Table 3. *Prognostic factors for influenza-related hospitalization and death in patients under and over 65 years of age*

Characteristic	18–64 years ($n = 112$)			⩾ 65 years ($n = 203$)		
	Cases ($n = 36$) No. (%)	Controls ($n = 76$) No. (%)	Adjusted OR (95% CI)	Cases ($n = 83$) No. (%)	Controls ($n = 120$) No. (%)	Adjusted OR (95% CI)
NHS insurance*	31 (86)	49 (65)	8·8 (1·1–73)	72 (87)	84 (70)	3·1 (1·6–8·5)
COPD†	10 (28)	14 (18)	15·6 (2·1–120)	14 (17)	16 (13)	2·1 (0·7–6·1)
CHF†	1 (3)	—	—	8 (10)	7 (6)	2·6 (0·7–9·4)
> 1 high-risk disease‡	15 (42)	8 (11)	24·9 (2·8–223)	35 (42)	27 (23)	2·2 (0·9–5·5)
⩾ 5 GP consultations¶	21 (58)	29 (38)	1·1 (0·2–5·7)	52 (63)	39 (33)	3·0 (1·4–6·7)
Previous hospitalization§	15 (42)	8 (11)	6·8 (1·2–39·4)	21 (25)	11 (9)	1·5 (0·6–3·8)
No. drugs (x, S.D.)	3·6 (1·6)	2·1 (1·5)	1·4 (1·0–2·1)	3·5 (1·5)	2·4 (1·5)	1·3 (1·0–1·7)
Vaccinated in 1996‖	32 (89)	65 (86)	0·7 (0·1–4·7)	73 (88)	110 (92)	0·9 (0·3–3·0)

* Versus private insurance.
† Versus other high-risk disease.
‡ Versus one high-risk disease.
¶ Versus 1–4 GP consultations.
§ Versus no hospitalization.
‖ Versus no vaccination in 1996.

of the outcome parameter) after adjustment for all other prognostic factors in the model.

Table 2 also shows results of the subgroup of certified cases and their controls. Except for the indicator previous hospitalization and NHS insurance, point estimates of adjusted relative risks are similar or somewhat higher than those assessed in all cases and controls.

When analysed according to age, most associations appeared stronger in patients aged 18–64 years (Table 3). Much stronger associations were observed for the prognostic factors NHS insurance, presence of COPD, more than one high-risk condition and current immunization against influenza.

DISCUSSION

Our study showed that routinely obtained clinical information on patients in the community with chronic medical disorders can be used to predict influenza-associated hospitalization and death during epidemics given an influenza vaccination rate in these groups as high as 90%. Moreover, the identified prognostic factors appeared to be even more strongly related to development of serious complications of influenza in those under 65 years of age. These results can facilitate reaching most vulnerable patient groups for additional preventive or therapeutic measures by physicians in both primary and secondary care and information is important for winter hospital admissions planning. Also, identified factors may be valuable indicators that should be controlled for in case of presence of prognostic dissimilarities among exposed and non-exposed in future non-experimental evaluations of anti-influenza agents such as neuraminidase inhibitors.

A limitation of our study is that diagnostic uncertainty in primary care may have induced biased associations. The case-definition used included various acute diseases as diagnosed by GPs. Nichol and colleagues have stressed that the full range of complications potentially associated with influenza including respiratory, cardiac and diabetes complications should be taken into account when evaluating vaccine effectiveness [14]. It is, however, unlikely that systematic error resulting from diagnostic bias in the study base was present since overall point estimates of associations were similar in the analysis restricted to specialist-confirmed cases with their controls. Although virological confirmation of influenza virus infection was not available for cases, we believe that influenza was directly or indirectly involved in many complications. Limitation of case detection to the weeks in which influenza A and B were highly epidemic according to reported incidence of influenza-like illness from Dutch sentinel practices, the temporal correlation between case-incidence and influenza-like illness during the surveillance period, and the observation that other viruses like the respiratory

https://doi.org/10.1017/S0950268801005180 Published online by Cambridge University Press

syncytial virus may be relatively less prevalent when influenza activity is peaking, support this contention [12].

Our study lacked adequate power to detect a statistically significant reduction in serious complications resulting from influenza vaccination in this population with very high vaccination rates. Nonetheless, our data indicate that a 10–30% reduction of complications may be achieved with the conventional trivalent influenza vaccine. These estimates are in agreement with earlier reports and tend to underestimate the true reduction of complications in the absence of virological confirmation [14–18].

The study domain of our case-control study was limited to patients with current high-risk morbidity. Although an age-based influenza vaccine policy was demonstrated effective and cost-saving [14], we believe that the impact of additional measures against influenza and its complications can be most effectively increased through reaching the most vulnerable patients with these conditions.

Our study is unique in that we determined prognostic factors in a non-selected outpatient group with a high influenza vaccination rate. Nonetheless, our findings are in accord with results of the few earlier studies that provided information on clinical determinants of potentially influenza-associated disease although different populations were examined and influenza immunization rates were much lower. Ohmit and Monto, for example, estimated similar relative risks in those with pulmonary or cardiac disease as observed in our study, although underlying disease was self-reported by patients and aggregated to large disease-categories [18]. Fleming and colleagues observed increased risks for primary care patients with chronic pulmonary disease, but not for those with cardiac disease [19]. In their study, GP medical records were available for 50% of cases that were originally identified which may have masked the role or some prognostic factors we observed in our study. In elderly and those with cardiac, pulmonary and more than one high-risk disease, Barker and colleagues observed increased risks of pneumonia and influenza deaths [20]. No information was present, however, on primary-care based prognostic indicators such as GP visits and previous hospitalization. In a large hospital-based study, Glezen and colleagues observed pulmonary disease being the most important prognostic variable for hospitalization due to acute respiratory disease as was cardiac disease for death during influenza epidemics [21]. Furthermore advancing age was associated with higher hospitalization rates. However, inferences from the data were hampered by a lack of a control group. Paul and colleagues showed influenza-related febrile illness to be more common among patients with pulmonary disease than others, but in patients with cardiac disease and with previous hospitalization such an increased risk was not observed [22]. In their study, information was collected from clinic charts which may lack valuable information on other primary care-based factors.

Among the non-modifiable prognostic factors that were associated with the case status in our study, few were unexpected. Polypharmacy should be considered an indicator of severe underlying disease. In the elderly Dutch population, two-thirds of persons are insured through the National Health Insurance. NHS insurance status was much more prevalent in cases than controls and is considered an important indicator of lower social economic status of patients. In addition, patients with COPD and those with heart failure appeared to be more at risk than asthmatics or those with other cardiovascular disease including previous myocardial infarction. Most likely, the condition of these specific patient groups is most prone to exacerbations resulting from viral infections. In addition, a high GP visiting rate has been an important prognostic indicator in many community- and primary care-based studies among various disease categories [14–16, 23]. In an earlier influenza vaccine cost-effectiveness study among the high-risk segment of patients with chronic lung disease we also found that 90% of hospitalized patients had COPD, heart failure or a high GP visiting rate [23]. Interestingly, the same indicators are of particular importance in adult patients under 65 years. In the elderly, ageing and underlying disease are strongly associated with poorer immunity against viruses whereas in younger patients underlying disease might mainly be responsible for development of complications. This finding supports current immunization recommendations [5, 6].

In establishing unbiased estimates of clinical effectiveness of preventive measures and therapy, community-based pragmatic experiments are considered most rigorous [24]. However, scientists face major problems in the design of such investigations mainly because of ethical issues, sample size limitations and unpredictability of influenza occurrence [25]. Therefore, many non-experimental intervention studies have been carried out [14–18, 21, 23, 25]. More are to be

expected among different target groups and effectiveness of other anti-influenza agents as newly developed vaccines as well as prophylactic drugs may be evaluated in the same way. However, since comparability of prognosis among exposed and non-exposed persons at baseline can be fully achieved by randomization only, non-experimental studies are threatened by confounding bias. Clinical and non-clinical factors may influence vaccine uptake leading to so-called 'confounding by indication' [24]. Consequently, the validity of study results depends on the availability of information to control for inequality in baseline prognosis. Information on prognostic indicators from our study may be used to more validly assess clinical effectiveness of influenza prevention in non-experimental studies.

In conclusion, since the health-economic consequences of influenza infection are considerable, several identified prognostic clinical indicators of increased risks for serious complications can be used to improve influenza prevention or early treatment among most vulnerable patient groups.

ACKNOWLEDGEMENTS

We kindly acknowledge the participating GPs for their contribution to the identification of cases and data collection. We are also thankful to P. Zuithoff for valuable advice on the statistical part of the study.

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