Effectiveness and implementation of influenza vaccination

A non-experimental approach

E. Hak

The realisation of this thesis took place at the Julius Center for General Practice and Patient Oriented Research, University Medical Center Utrecht, the Netherlands.

The author wishes to thank the Departments of Pulmonology and Virology of the UMC Utrecht, the Laboratory for Clinical Vaccine Research of the National Institute of Public Health and the Environment, Bilthoven, the Centre of Quality of Care Research of the Catholic University of Nijmegen, the VA Medical Center, Minneapolis, HealthPartners Research Foundation, Minneapolis, Kaiser Permanente Northwest, Portland, Oxford Health Plans, New York and the Centers for Disease Control and Prevention, Atlanta for their kind collaboration in the studies presented in this thesis.

The studies were financially supported by grants from the Netherlands Asthma Foundation (No. 97.51), the Dutch Ministry of Health and Welfare and the University Medical Center Utrecht.

Financial support by the Netherlands Asthma Foundation, Wyeth, GlaxoSmithKline and the UMC Utrecht for the publication of this thesis is gratefully acknowledged.

Cover design: Rob van Doornik
Lay out: Hedie von Bannisseht, AV dienst UMC Utrecht
Printed by Drukkerij Zuidam en Uithof BV, Utrecht

CIP gegevens Koninklijke Bibliotheek Den Haag

E. Hak. Effectiveness and implementation of influenza vaccination. A non-experimental approach
Thesis Utrecht University - with references- with summary in Dutch

ISBN 90-393-2783-1

Key words: influenza, immunization, prevention, general practice, methodology, asthma, COPD

Effectiveness and implementation of influenza vaccination

A non-experimental approach

Effectiviteit en implementatie van influenzavaccinatie

Een niet-experimentele benadering
(Met een samenvatting in het Nederlands)

Proefschrift

Ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de Rector Magnificus, Prof. dr. W.H. Gispen,
ingevolge het besluit van het College voor Promoties
in het openbaar te verdedigen op
dinsdag 11 september 2001 des namiddags te 16.15 uur

door

Eelko Hak
geboren op 7 december 1968 te Vlaardingen

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CHAPTER I

Introduction

Influenza pandemic: the Spanish flu.

'The world was at war in 1918. Millions of troops were fighting a largely ground struggle in Western Europe. Influenza was first reported in March 1918 from fort Riley, Kansas, United States. The virus appeared to have swept the world in three waves over less than two years' time, gaining virulence with each new assault. Crowding in the military was responsible for high attack rates reported a month later. Forty percent of US Navy personnel became ill. There were 54,000 battle deaths among US forces and 43,000 influenza and pneumonia deaths. By October 1918 its strength was so great that people died with spectacular speed. Influenza led to cyanosis and death from pneumonia within 2 to 3 days of onset. There were even reports of women boarding a New York subway feeling little else than mild fatigue and being found dead when the train stopped 45 minutes later. In New York alone, over 20,000 citizens died. In two months time, 1 in 130 citizens of Philadelphia died from influenza. Disease was reported across Europe in May, in Africa in June and India and China in August. In times of steamships and horses influenza had circled the globe in less than 5 months. Estimates of the total number of deaths worldwide vary from 20 to 40 million leading to social disruption including a shortage of coffins.'

Photo: http://www.pbs.org/wgbh/amex/influenza, accessed March 12th, 2001

Text modified from: *Garrett L. The coming plaque. New York: Penguin books USA Inc, 1994 and Steinhoff M. Epidemiology and prevention of influenza. In: Nelson KE, Masters Williams C, Graham NMH (eds.). Infectious Disease Epidemiology. Aspen Publishers, Inc.: Gaitersburg, Maryland, 2001*

Introduction

The burden of influenza

The unique epidemiology of the influenza virus is characterized by winter epidemics of respiratory disease in temperate climates circulating globally with attack rates of 10 to 30 percent. In the United States and the Netherlands, 20,000 cases and 2,000 excess deaths occur during influenza epidemics every year.[1,2] Also, the virus has caused three global pandemics in the 20th century.[3] Pandemics occur once every 30 to 40 years and the pattern is characterized by a start from a single location and global spread along the travel routes. Influenza pandemics are responsible for millions of hospitalizations and deaths worldwide.

The high mutability of its antigens is the key to its ability of the virus to cause annual epidemics and periodic pandemics. Influenza A, categorized into subtypes according to their hemaglutinin (H) and neuraminidase (N) components, and influenza B are the two main types causing human infections. Infection occurs in all age groups, but the infection rates are highest among children, while serious disease and mortality mainly occur among the elderly and those with high-risk medical conditions, regardless of age.[4]

The main transmission route is from person to person by droplet spread containing up to 10^5 virus particles/ml.[5] The incubation period is short, averaging two days, and people may be infectious before any symptoms appear. Uncomplicated influenza is characterized by sudden onset of fever, headache, cough, myalgia, or other constitutional symptoms.[6] Gastrointestinal symptoms sometimes accompany respiratory symptoms in infants and children. Usually, influenza is self-limiting, lasting 3 to 5 days. By disruption of epithelia of the respiratory tract and decreased mucociliary clearance, it can predispose to complications such as otitis media,[7] exacerbations of underlying lung disease[8] or cardiac disease[9] and viral or secondary bacterial pneumonia[10-12] often needing hospitalization and sometimes fatal.[4] Since the changes in antigenic make-up of the virus are unpredictable,[13] the influenza virus will continue to exact its toll of morbidity and mortality unless preventive and therapeutic measures targeted at those who need them are implemented.

Prognosis of influenza

As preventive health care budgets are limited, large-scale measures for the control of influenza should focus on individuals with a high probability of developing complications from it. The available methodology commonly used to study the prognosis of influenza in the community include cohort and case—control studies. In the time before large-scale influenza vaccination was

introduced,[14,15] or when vaccination rates were still relatively low,[16-19] some studies focused on establishing risk factors for serious outcomes such as need for hospitalization for influenza and pneumonia, or deaths from all causes during epidemics. More recent prognostic information has been acquired through non-experimental vaccine effectiveness studies.[20-25] Factors that have consistently been shown to be independently related to increased risk of such outcomes include age (notably infants and young children[18,19] and the elderly[20-25]), underlying disease (e.g. chronic cardiac, pulmonary or metabolic disease; renal dysfunction; hemoglobinopathies or immune-suppression),[4] pregnancy[26] and place of residence during epidemics (nursing home or hospital).[27,28]

Limitations of current prognostic evidence

Several potential limitations need to be considered when trying to use currently available prognostic evidence from existing studies in clinical practice. Firstly, the statistical analyses employed in all studies were incomplete —though most used logistic regression analysis techniques to assess the independent associations of potential risk factors with the relevant end point, none extended the analysis by developing a clinical prediction rule to estimate the probability of an individual having that end point.[29] Data on individual absolute risks of complications are, however, essential for development of efficient preventive and therapeutic measures. Secondly, most of these studies were conducted in North-America. In Europe, general practitioners have a pivotal role both in delivering health care and in selection of patients for secondary or tertiary care. The results of the few prognostic studies carried out in European countries[21,25] differ from those from North-America.[14-20,22-24,26] The absence of studies on determinants of endpoints other than the serious complications death or admission to hospital for influenza or pneumonia is another limitation. Some studies, for example, have shown that during influenza epidemics the incidences of exacerbations of chronic pulmonary disease,[12,30-32] deterioration of metabolic control in diabetes[33] or acute cardiac disease[34,35,9] are associated with the incidence of influenza in the community. However, the risk of these complications that is attributable to influenza infection is largely unknown.

Options for the control of influenza

The main direct option for reducing the impact of influenza is immunoprophylaxis with conventional inactivated (i.e. killed-virus) vaccine.[4,36] Other options include immunoprophylaxis with intranasally administered cold-adapted live-attenuated influenza virus vaccines,[7,37] and use of antiviral drugs such as amantadine and rimantadine, or neuraminidase inhibitors such as zanamivir and oseltamivir. The first antiviral drugs are effective against

influenza A only and can cause considerable adverse effects.[38] Treatment with zanamivir[39,40] or oseltamivir[41] reduces the course of influenza infection by 1 to 1.5 days. Preventive use of these latter neuraminidase inhibitors reduces the occurrence of influenza illness by 30 up to 89 percent, [42-44] similar effects as the conventional influenza vaccination in healthy persons.[45] Although it might be expected that prophylactic use of neuraminidase inhibitors increases protectiveness against influenza when given simultaneously with influenza vaccination, no effectiveness studies have been carried out among the current vaccine target population. Another major constraint on using these drugs is the difficulty of making an accurate diagnosis of influenza in time to be of value.[36] In the Netherlands, these drugs are therefore not recommended for large-scale use for either prophylaxis or treatment.

Conventional inactivated influenza vaccine

According to the recommendations of the World Health Organization, the conventional vaccine contains two types A strains and one type B strain forecast to be the most likely to circulate in the coming winter.[4] The current vaccine is made from virus grown on embryonated eggs. After ultra-centrifugation, virus particles are highly purified and then killed by formaldehyde. Virus mutation by antigenic drift and shift means that a new vaccine needs to be developed each year. The essential data to predict likely new strains are produced by a global network of surveillance laboratories.[46] The development process takes up to six months which is short enough to prepare for regular epidemics, but too long for response to a potential pandemic.[47] Therefore, other vaccine production processes are being developed to enable a higher production capacity.

Influenza vaccine efficacy and effectiveness

In general, epidemiological studies on the impact of vaccines distinguish two measures: vaccine efficacy and vaccine effectiveness.[48] Vaccine efficacy is commonly assessed in pre-marketing randomized double-blind placebo-controlled clinical trials. The most frequently used clinical endpoints in such trials include post-vaccination protective antibody titers as a measure of indirect protection and influenza infection rates as a measure of direct protection. Study populations include healthy people and sometimes patients in a limited range of high-risk categories. In influenza vaccine trials, most vaccinated children and young adults developed protective antibody titers against influenza with strains similar to vaccine components.[45,49,50] Some studies suggest that elderly persons[51] and patients with certain chronic diseases[52,53] (the most important subgroup to target for vaccination) may develop lower titers. Only one randomized placebo-controlled trial has been conducted to establish clinical direct effects of vaccination among healthy elderly people.[54] In this Dutch

study by Govaert et al. the vaccine appeared to reduce the incidence of serologically confirmed influenza by 50%.

For overall protective clinical effect in routine clinical practice calculated from post-marketing studies the term 'vaccine effectiveness' is often used. Influenza vaccine effectiveness is the result of both the vaccine's direct effect, which refers to the ability of the vaccine to protect the individual against clinical influenza infection and its complications, and the indirect effect, which refers to reduction of the spread of influenza in the population. This latter effect is one of the reasons to vaccinate persons in closed communities such as nursing homes,[27] health care institutions[28] and day-care for children.[55] Vaccine effectiveness can be estimated using post-marketing study designs including pragmatic randomized controlled trials, cohort and case—control studies incorporating clinical end points relevant to the individual patient. In cohort studies, vaccinees and non-vaccinees are followed up retrospectively or prospectively and incidences of complications of influenza in both exposure groups are compared. The common measure of association is the incidence rate ratio which may be considered as a relative risk (RR). In case—control studies, frequency of exposure, i.e. vaccine use, in cases and controls (randomly sampled from the study base) is compared. In these case—control studies, the common measure of association is the odds ratio (OR) or, in case of a matched design, the ratio of discordant pairs. In general, vaccine effectiveness in percent is given by 1—RR*100 in trials and cohort studies or 1—OR*100 in case—control studies.[5]

In contrast to the scarcity of large randomized placebo-controlled trials with clinically relevant endpoints, there are many published non-experimental studies on influenza vaccine effectiveness. Gross et al. have summarized the results of 20 such studies carried out among the elderly.[56] The pooled estimates of vaccine effectiveness were 56 percent (95 percent confidence interval 39 to 68 percent) for preventing respiratory illness, 53 percent (35 to 66 percent) for preventing pneumonia, 50 percent (28 to 65 percent) for preventing hospitalization and 68 percent (56 to 76 percent) in preventing death. One of the key studies on the vaccine's effectiveness on severe end points was a serial prospective cohort study among the elderly by Nichol and colleagues.[20] In this study, more than 25,000 elderly non-institutionalized seniors were followed up using medical databases during three consecutive influenza periods. The overall vaccine effectiveness in reducing the incidence rates of death or hospitalization for pneumonia or influenza appeared to be between 48 and 57 percent. In another earlier case—control study, Fedson and colleagues observed reductions in hospitalizations for pneumonia or influenza of between 29 and 32 percent,

and reductions in mortality from all causes of between 27 and 30 percent among persons aged 45 years or older.[23] Another key study published by Ahmed and colleagues estimated a 41 percent reduction in mortality from all causes in a case—control study among subjects aged 16 years or older, mostly elderly.[57] Most subsequent studies among the elderly confirmed the vaccine's effectiveness in reducing serious complications such as need for hospitalization for influenza or pneumonia, or death with estimates varying from 40 to 60 percent.[22,25,58]

Limitations of current evidence for influenza vaccine effectiveness

The various limitations in validity and applicability of the results of the existing studies might, however, have led to sub-optimal clinical guidelines for influenza control. One of the major drawbacks of non-experimental evaluation studies of drugs is the potential for 'confounding by indication'.[59] Vaccinees and non-vaccinees are not randomly selected and in practice these groups differ with regard to average prognoses. In health care systems with a strong primary care component, vaccinees tend to have more risk factors than non-vaccinees. Unadjusted effectiveness estimates might therefore obscure a potential positive effect of the vaccine or at least underestimate its true protectiveness. Although most studies have controlled for the presence of these confounding factors by applying regression techniques, other techniques in the design or data-analytical phase of the study such as restriction of the study population or the design of a quasi-experiment using propensity scores[60] have not often been used for further control for residual confounding.

Other validity issues, particularly with case—control studies, include potential information bias and selection bias.[61] The first refers to differing information on cases and controls regarding the presence of vaccination or prognostic variables. The use of medical databases greatly reduces such information bias and most large-scale studies have therefore collected data by review of computerized patient records. Selection bias may be present when cases or non-cases are selected on the basis of their vaccination status. To prevent differential selection of outcomes for vaccinees and non-vaccinees, the case definition should be strictly applied. Therefore, most studies use death or hospitalization for influenza or pneumonia as the main endpoints. However, potential invalidity of study results remains a concern and authors should carefully discuss potential sources of bias in their study.

Finally, most vaccine effectiveness studies were conducted among the elderly or institutionalized populations. Only few were carried out among children with chronic high-risk disease and they were small, and covered one influenza season

only. In studies including infants and children, the vaccine reduced the occurrence of episodes of otitis media by 40 percent[7,62,63] and the number of febrile influenza episodes among young asthmatics by 49 percent.[64] Among the large group of patients with high-risk disease of working-age no such clinical benefits from influenza vaccination have been reported so far and studies are therefore needed.

Adverse effects of influenza vaccination

The literature on the potential adverse effects of the vaccine is vast. Local reactions such as soreness at the site of vaccination usually lasting about two days occur in 10 to 64 percent of patients.[4,36] Severe systemic reactions may occur in patients who are hypersensitive to egg-allergens, so egg hypersensitivity is a contra-indication to conventional influenza vaccination, though in practice it is very rare. Although an association with Guillain-Barré syndrome has been put forward,[65,66] this risk, if present, is as low as one in a million. In all, the conventional influenza vaccine may be considered safe, even in combination with routine child vaccinations or pneumococcal vaccines.[67]

Implementation of a population-based influenza vaccination program and coverage

Epidemiological studies among the elderly and few among high-risk children have demonstrated a high impact of influenza and clinical benefits of annual influenza vaccination. Further knowledge on the barriers to implement an immunization program is required to be able to effectively control its public health burden.[68] To develop and maintain an effective preventive program, clear clinical guidelines for care-givers are needed.[69] As a first step, the Dutch Health Council followed by the Dutch College of General Practitioners summarized evidence for the need for control of influenza by annual immunization against influenza.[70] Furthermore, numerous studies on the acceptance of influenza vaccination among patients have shown that non-compliance with annual vaccination programs is mainly associated with lack of personal recommendation by a physician, lack of awareness of the risks of influenza and fear of adverse effects.[71-74] Educational programs are therefore needed to reach and convince both physicians and high-risk subjects of the health benefits of vaccination. Finally, logistical problems inherent in vaccine supplies should be minimized, and selection of high-risk people for vaccination should be facilitated. In the Netherlands, general practitioners play a key role in the health care delivery. Almost all Dutch inhabitants are registered with a GP. Also, more than 80% of Dutch GPs record all patient contacts in computerized medical records. Facilities for computerized selection of high-risk patients and administration of the preventive services are therefore easily available. GPs are

thus in a unique position to target preventive care, especially immunization programs, to those who need it. A small-scale experimental study carried out in 1993 demonstrated that an educational program aiming at GPs to set up a step-wise influenza vaccination program was successful in increasing influenza vaccination coverage among their vaccine target population.[75] Based on this study and other educational studies,[69,76] the Dutch Ministry of Health, Sports and Welfare decided in 1995 to provide financial support for a nationwide preventive program called 'Tailor-made prevention' to educate GPs and facilitate preventive tasks including influenza vaccination.

Outline of this thesis

The three parts of this thesis aim at filling some essential gaps in our scientific knowledge on (I) prognosis of influenza, (II) vaccine effectiveness in high-risk subgroups and (III) effects of implementing a nationwide primary care based influenza immunization program.

Part I. Prognosis of influenza
In chapter 2 we aim at identifying prognostic factors for influenza-associated death and/or admission to hospital in Dutch adults with high-risk medical conditions who require influenza vaccination. We specifically address the potential modification by age of associations of patient factors with the end points among patients of working-age as compared with the elderly. In chapter 3, we describe how a large-scale influenza vaccination monitoring and evaluation program covering non-institutionalized elderly people in three geographically disparate Health Maintenance Organizations (HMOs) across the United States enabled us to develop and validate a clinical prediction rule for the need for hospitalizations for influenza or pneumonia, or death from all causes.

Part II. Clinical effectiveness of influenza vaccination
In chapter 4 we elaborate on 'confounding by indication' in non-experimental evaluation of influenza vaccination as one of the major methodological problems of using cohort and case—control study designs. We also suggest some tools to reduce the impact of such bias and illustrate the effects of some of these options with part of the data from the study described in chapter 6. In chapter 5 we describe a serial retrospective cohort study aimed at establishing the potential clinical benefits of annual influenza vaccination among children with asthma. This study covered the 1995/96 and 1996/97 influenza A epidemics.

In chapter 6 we present the results of a prospective cohort study among patients with asthma or COPD aged 18 years or over during the 1995/96 influenza A epidemic. In this study we determined the occurrence of influenza-associated morbidity and mortality and clinical benefits of influenza vaccination with particular emphasis on the potential modification of vaccine effects by age (18 to 64 years versus ≥65 years). In chapter 7 we report our serial prospective nested case—control study among asthma and COPD patients of working-age to determine the occurrence of influenza-associated respiratory and cardiac morbidity and mortality, and the effect of influenza vaccination in reducing these complications. Study subjects were followed during the 1998/99 influenza type B epidemic and the 1999/2000 influenza A epidemic. In chapter 8 we assess the influence of various high-risk medical conditions on the effectiveness of influenza vaccination among non-institutionalized elderly members of three large HMOs. The observations of this prospective cohort study covered the 1996/97 and 1997/98 influenza A epidemics in the United States.

Part III. Implementation of influenza vaccination

In chapter 9 we report the collection of baseline data from a random sample of Dutch GPs before the nationwide introduction of the 'Tailor-made prevention' program. In this study we assessed independent characteristics predicting a high overall immunization rate. In chapter 10 we evaluate whether the introduction of a computerized influenza prevention module in a general practitioner information system facilitates the various logistical aspects of the influenza immunization program in Dutch general practice. In chapter 11 we present data of an uncontrolled before-and-after trial on the effects of a coordinated nationwide program called 'Tailor-made prevention' that aimed at improving influenza immunization practice in the Netherlands.

The thesis ends with a general discussion of our findings with respect to implications for future control of influenza-related morbidity and mortality. In addition, this last chapter provides suggestions for further study into various aspects of this major and continuing public health issue.

Essential issues dealth with in this thesis

What is already known?	What is largely unknown?	Chapter
Part I. Prognosis of influenza		
Influenza affects persons of all ages	The incidence of complications other than hospitalization for influenza or pneumonia, or death	5, 6, 7
Infection rates are highest among children	The occurrence of influenza-associated morbidity and mortality in children and patients with high-risk conditions of working-age	5, 6, 7
Complications of influenza infection include lower respiratory tract infections, acute cardiac disease, diabetes events and death	The extent to which prognostic factors are associated with rare influenza complications and whether age modifies the associations	2, 3
Patients with certain medical conditions, elderly, pregnant women and people in institutions are at high risk for complications of influenza	The absolute risk of an individual's developing complications from influenza and whether a clinically useful prediction rule can be developed	3
Part II. Clinical effectiveness of conventional influenza vaccination		
Most evidence is acquired through non-experimental studies.	Whether 'confounding by indication' can be adequately prevented or limited	4
Influenza vaccination reduces respiratory illness, influenza and pneumonia hospitalizations and death in the elderly by 30% to 50%	The reduction of influenza-associated respiratory morbidity in high-risk children and patients of working-age	5, 6, 7
Influenza vaccination might lead to lower protective antibodies in elderly persons and persons with high-risk medical conditions	Whether specific high-risk medical conditions or age influence the vaccine's efficacy	6, 8
Part III. Implementation of influenza vaccination		
Clinical guidelines are essential for effective preventive care	To what extent Dutch GPs follow the influenza vaccination guidelines	9
Personal reminders by physicians increase the acceptability of vaccination by the vaccine target group	Which practice and organizational characteristics in Dutch general practice predict optimal immunization rates	9
Immunization practice might efficiently be implemented in primary care	Whether computerized facilitation modules effectively increase vaccine coverage	10
Educational efforts should focus on misconceptions about influenza risks and vaccine effectiveness	Whether a large-scale multi-faceted educational program could succeed in improving immunization practice in primary care	11

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CHAPTER 2

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

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

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 1996/97 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 facilitate targeting additional preventive or therapeutic measures at the most vulnerable segment of the vaccine target group.

Key-words: influenza, vaccine, prevention, general practice, effectiveness, epidemiology

Published as: Hak E, Verheij ThJM, Essen GA van, Lafeber AB, Grobbee DE, Hoes AW. Prognostic factors for influenza-associated hospitalization and death during an epidemic. *Epidemiol Infect*, 2001;**126**:261-8

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 most likely developing 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 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 program 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

Setting and design

Our study is part of an evaluation of the nation-wide intervention program '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) centers 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 centers were spread all over the Netherlands and relevant anonymous data were supplied by GPs to the data-management center of the Julius Center, University Medical Center Utrecht.

We designed a case-control study nested in the primary care centers' 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 18,163 patients with registered codes indicating potential high-risk disease among the total vaccine target population including healthy elderly (n=32,425 persons).

Identification of hospitalized and fatal cases during 1996/97 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 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 program.[8] The trivalent sub-unit 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 two 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 chi-square 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 modeling 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 analysis (8 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 percent.

Results

Mean age of the patient cohort of 18,163 persons was 62 years (SD 18, range 18-102 years) and 49 percent were male. Based on coded entries, cardiovascular and pulmonary disease appeared present in 36 and 32 percent, 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, eight (7%) from pneumonia, eight (7%) from myocardial infarction, five (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 (SD 14 years) and 55% was 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 (20% reduction of the outcome parameter) after adjustment for all other prognostic factors in the model.

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

	Cases		Controls	
Characteristic*	**No.**	**%**	**No.**	**%**
Age ≥ 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
≥1 high-risk disease	50	42	35	18
GP visits				
1-2	26	22	78	40
3-4	20	17	50	25
≥ 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.

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.

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, SD)	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

When analyzed 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 and more than one high-risk condition.

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

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

	18-64 years (n =1 12)					≥65 years (n = 203)				
Characteristic	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	(69)	3.1 (1.6-8.5)
COPD†	10	(28)	14	(18)	15.6 (2.1-120)	14	(17)	16	(16)	2.1 (0.7-6.1)
CHF†	1	(3)	-		-	8	(10)	7	(5)	2.6 (0.7-9.4)
> 1 high-risk disease‡	15	(42)	8	(11)	24.9 (2.8-223)	35	(42)	27	(16)	2.2 (0.9-5.5)
≥ 5 GP consultations¶	21	(58)	29	(38)	1.1 (0.2-5.7)	52	(63)	39	(36)	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, SD)	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

such 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 influenza vaccination or 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 et al. 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 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 to 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 resulting from 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 et al. 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. Paul et al. showed influenza-related febrile illness to be more com-

mon 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 poorer immunity against viruses are strongly associated with increased risks for morbidity from influenza 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 to design 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 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.

Acknowledgment

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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CHAPTER 3

A clinical prediction rule for pneumonia and influenza hospitalization and death during influenza epidemics

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A clinical prediction rule for pneumonia and influenza hospitalization and death during influenza epidemics

Background Uncertainties among providers and patients about a patient's risk for serious influenza associated complications and the potential benefits from vaccination may contribute to unsatisfactory low influenza vaccination rates. In order to quantify risk for serious outcomes during influenza seasons, we developed a clinical prediction rule for the probability of pneumonia or influenza associated hospitalization or death among seniors.
Methods We developed the clinical prediction rule using data from linked, administrative databases on 16,280 non-institutionalized and unvaccinated seniors. Validation of the rule was conducted in five unvaccinated and six vaccinated additional cohorts of more than 11,000 elderly members of three managed care organizations. Using logistic regression analysis, the following predictors were selected: age, gender, presence of pulmonary, cardiac and renal disease, dementia/stroke and cancer, number of outpatient visits and hospitalization for pneumonia and influenza in the previous year.
Results Reliability of the regression model was good (goodness-of-fit test, p=0.64) and it discriminated well between those with and without the combined end point (area under the receiver-operating curve 0.83, 95% CI 0.81-0.85). Validation revealed moderately lower but acceptable discriminating values between 0.72 and 0.81. The prognostic accuracy of the prediction rule in the derivation cohort was high when a cut-off sum-score ≥50 points, reflecting a predicted probability ≥1.0%, is chosen (subjects with end point vaccinated: 89%, without end point unvaccinated: 51%) while only 50% of seniors would be selected for vaccination. The influenza vaccine reduced hospitalization or death by 43% (95% CI 39% to 47%) in subjects with a high score (≥50 points).
Conclusions The prediction rule may be useful to make sure that at risk seniors are vaccinated and to target additional measures for vaccination to those most likely to benefit.

Key words: influenza, immunization, elderly, administrative database, epidemiology

Submitted as: Hak E, Wei F, Nordin J, Mullooly J, Poblete S, Strikas R, Nichol KL.
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Influenza continues to cause considerable morbidity and mortality worldwide.[1] In the United States, it is estimated that influenza is responsible for hundreds of thousands of hospitalizations,[2] tens of thousands of deaths[3] and billions of dollars in excess costs.[4] Most of the excess morbidity and mortality occurs among the elderly. To reduce these consequences of influenza, recommendations include yearly vaccination of vulnerable patient groups.[5,6]

Although influenza vaccination is effective in reducing morbidity and mortality,[7-10] and cost-saving among the elderly,[11] nearly 40 percent of this

target population fail to receive the vaccine each year.[5] Vaccination rates for high-risk persons under 65 are even lower. Uncertainties among providers and their high risk patients about the risk of serious, influenza related, complications and benefits of vaccination may contribute to these low vaccination rates. Recent data from a survey of Medicare beneficiaries, for example, suggest that lack of awareness of personal risk is among the most common reasons for failing to receive the influenza vaccine.[12]

Another recent issue attracted attention to a higher need for individual risk stratification. In a notice to readers, physicians were urged to identify high-risk persons because a shortfall of the influenza vaccine was expected for the 2000-2001 season.[13] This might happen more often during coming influenza seasons and in case of a pandemic a substantial delay or shortfall of vaccine will likely occur as well in which information on a patient's risk will undoubtedly be of use.[14]

For these reasons a careful risk assessment using an accurate, objective model of prognosis could help physicians assess risks of individual patients and improve the decisions about immunization and additional care. We assessed the prognostic value of clinical information derived from administrative databases of three health plans to develop a prediction rule for the probability of hospitalization for pneumonia and influenza and all-cause death during influenza epidemics among non-institutionalized persons over 65 years of age. We further demonstrated performance of the model when applied to our patients and the consequences of its use in future populations.

Methods

Setting

This study is part of an ongoing collaborative effort between three large managed care organizations from geographically disparate locations across the US to pool data derived from their linked medical databases in order to provide assessments of impact of influenza and the health and economic benefits of vaccination among members of their health care plans. HealthPartners (HP) is a nonprofit health maintenance organization with about 890,000 members in Minnesota and Wisconsin. It offers coverage for 280,000 members through a staff model HMO, while the other members are covered through a network HMO model. Kaiser Permanente Northwest Division (KPNW) provides medical care for nearly 420,000 persons in the Portland, Oregon-Vancouver and Washington regions. Oxford Health Plans (Oxford) provides health benefit

plans to 1.8 million members in New York, New Jersey, Pennsylvania and Connecticut. In all, over 3 million members receive medical care from these health plans. The health plans used protocols specifying the same definitions of co-morbidity and outcomes and obtained all study data, including baseline information, vaccination status and outcomes from their linked, administrative and clinical databases.

Study subjects

All members of the three health plans, aged over 65 years as of October 1, 1996 in the first year and October 1, 1997 for the second year, continuously enrolled for 12 or more months prior to October 1 of each year and non-institutionalized were included. A large enrollment period was chosen to ensure valid prognostic information to derive and validate the regression model.[15] Institutionalized patients were excluded because vaccination status was unknown.

Definitions of potential predictors

After an extensive literature search, we selected 15 clinical characteristics that possibly could be related to serious clinical outcomes during influenza epidemics. At baseline, the following potential predictors were included: age, gender, and a hospitalization for influenza and pneumonia and number of outpatient visits in the previous year. Underlying disease of eligible subjects was classified into 11 non-mutually exclusive disease categories according to entries of relevant codes in the *International Classification of Diseases, Ninth revision, Clinical Modification* (ICD-9-CM) in outpatient clinic or hospital databases 12 months prior to October 1 of each year: (1) pulmonary disease (ICD-9-CM codes 011, 460, 462, 465-466, 480-511, 512.8, 513-517, 518.3 518.8, 519.9, 714.81), (2) cardiac disease (093, 112.81, 130.3, 391, 393-398, 402, 404, 410-429, 745-746, 747.1-747.49, 759.82, 785.2, 785.3), (3) diabetes/other endocrine disorders (250-251), (4) renal disease (274.1, 403, 580-591, 593.71-593.73, 593.9), (5) immune-deficiency/organ transplants (042, 079, 279, V08, V42) (6) non-hematological and hematological cancer (140-198, 199.1, 200-208), (7) anemia spleen (280-289, 759.0), (8) cirrhosis (571), (9) nutritional deficiencies (254-255, 259.2, 260-269), (10) dementia/stroke (290-4, 331, 340-1, 348, 438), and (11) vasculitis/ rheumatologic diseases (446, 710, 714-714.4, 714.8, 714.89, 714.9).

Influenza seasons and vaccination

During the 1996-97 and 1997-98 epidemic, influenza activity was widespread in most US states, exceeding baseline levels for more than 5 consecutive weeks.[16,17] Influenza periods were defined as follows on the basis of Centers of Disease Control (CDC) surveillance data: Year 1, HealthPartners November

22, 1996 through May 24, 1997, Oxford: October 5, 1996 through May 3, 1997. Kaiser: November 22, 1996 through March 22, 1997. Year 2, HealthPartners: December 7, 1997 through March 28, 1998, Oxford: November 23, 1997 through April 4, 1998, Kaiser: December 21, 1997 through March 7, 1998. Vaccination rates varied from 39% to 71% during the years in the different health plans.

End point

The combined end point was the occurrence of hospitalization for influenza or, its main complication, pneumonia (ICD-9-CM codes 480-487) or death from all causes during the studied influenza seasons.

Model development

To develop the model, we used the data on all eligible study subjects from the HealthPartners database that were enrolled in the first season and who were not vaccinated against influenza (n=16,280). Absence of a characteristic in the medical database was assumed to indicate no presence of the characteristic under study and therefore missing values were absent. Age was classified into the following 5 categories according to exponential increase in risk of outcomes: 65-69, 70-74, 75-79, 80-89, ≥90. Similarly, the number of outpatient visits during the prior 12 months was classified into 4 categories: 0, 1-6, 7-12, ≥13. Descriptive statistics as proportions and means (SD) using SPSS for Windows, version 9.0, (SPSS Inc., Chicago, Illinois, USA) were calculated to describe baseline characteristics in the two comparison groups (with or without end point). The construction of the prognostic model started with a univariate assessment of the prognostic effect of each characteristic separately as given in terms of odds ratio's (OR) and their 95% confidence intervals (95% CI) using logistic regression analysis. In the next stage we used multivariate logistic regression modeling with a backward elimination procedure to select those variables that were related to the outcome with a p-value <0.15 as a criterion for selection. We first used the continuous variables age and number of outpatient visits to ensure that the selection of the corresponding classified variables was independent of the choice of the cut-off values. Forward selection was additionally performed to verify whether any previously deleted potentially relevant characteristic was incorrectly eliminated from the model. Interaction between variables included in the model was assessed to determine deviations from the additivity assumption by including first-order interaction terms in the final model. For each patient we calculated the individual probability of the outcome from the final model (predicted probability).

Model evaluation

The reliability of the multivariate logistic regression model derived from the derivation set was determined by the Hosmer-Lemeshow goodness-of-fit statistic.[18] The area under the receiver-operating-curve (ROC) was used to assess the model's discriminative ability.[19] The ROC is a plot of the true-positive rate (sensitivity) and false-positive rate (1-specificity) which is evaluated for each cut-off point of the predicted probability. The area under the ROC can be explained as the probability that the logistic regression model will assign a higher probability of the outcome to a randomly chosen patient with an outcome (hospitalization/death) than to a randomly chosen patient without outcome. An area under the curve (AUC) estimate of 0.5 indicates no discrimination whereas an estimate of 1.0 indicates perfect discrimination. External validation of the model was performed by comparing the AUC values across the other 11 cohorts stratified by immunization status (no/yes), site (1,2,3) and year (1,2).

Development and applicability of the prediction rule

The regression coefficients of the derived multivariate model were used to construct the prediction rule.[20,21] The predicted probability of outcome equals $1/\ 1 + e^{-(LP)}$ where the linear predictor (LP) = -6.0906 + 0.4681×age-category + 0.2939×gender + 2.0872×previous P&I hospitalization + 0.3794× outpatient visits-category + 0.6012×lung disease + 0.1952×heart disease + 0.4135×renal disease/transplant + 0.7273×dementia/stroke + 1.5887×cancer. For practical interpretation we have chosen to multiply the regression coefficients by 30 and round them to form the score. All scores indicating the relative influence of the variable on the occurrence of the combined endpoint were added to form a sum-score and classified. For sum-score cut-off points the following test characteristics were calculated: positive predictive value, sensitivity, specificity, proportion of outcomes missed (1.0-sensitivity) and proportion of persons selected.

Vaccine effectiveness

To assess whether patients with high or low risk score could benefit from the influenza vaccine, we calculated the vaccine effectiveness for the seniors in both risk groups using logistic regression. In this analysis, the association of vaccination status as main explanatory variable with the dichotomous end point was assessed, independent of other predictors, site and year. Vaccine effectiveness (VE) was determined as 1- OR times 100 percent.[11] Absolute reduction (AR) per 1,000 vaccinees was calculated as the vaccine effectiveness (VE) times the incidence of the end point in non-vaccinees.

Results

Of the 16,280 study subjects of the derivation cohort, 399 were hospitalized or died during that season (2.5%); 122 (0.7%) were hospitalized for pneumonia or influenza and 287 (1.8%) died from all causes.

Table 1. Association of clinical characteristics with hospitalization and death in derivation set (n= 16,280). Percentages are given, unless stated otherwise

Characteristic	Patients with outcome (n=399)	Patient without outcome (n=15,881)	Univariate Odds ratio (95% CI)	Multivariate Odds ratio* (95% CI)	P-value
Demographics					
Mean age (SD), y	81 (8)	75 (8)	1.8 (1.6-1.9)†	1.6 (1.4-1.8)†	<0.001
Female	41	38	1.2 (1.0-1.4)	1.3 (1.1-1.7)	0.008
Prior health care use					
Previous P&I hospitalization	16	1	22.4 (16.3-30.6)	8.1 (5.7-11.5)	< 0.001
Mean (SD) no. outpatient visits	26 (27)	11 (14)	2.4 (2.1-2.7)†	1.5 (1.3-1.8)†	< 0.001
Co-morbidity‡					
Heart disease	50	24	3.2 (2.6-3.8)	1.2 (1.0-1.5)	0.10
Lung disease	40	14	4.1 (3.3-5.0)	1.8 (1.4-2.3)	<0.001
Dementia/stroke	31	9	4.6 (3.7-5.8)	2.1 (1.6-2.7)	<0.001
Renal disease	13	4	4.0 (2.9-5.4)	1.5 (1.1-2.1)	0.02
Cancer	12	2	6.8 (4.9-9.4)	4.9 (3.4-7.0)	<0.001
Diabetes	19	12	1.8 (1.4-2.3)	-	
Anemia	24	8	3.7 (2.9-4.7)	-	
Nutrional def.	5	2	3.7 (2.4-5.9)	-	
Vasculitis/rheum	3	2	1.3 (0.7-1.3)	-	
Immunedeficiency	2	1	2.0 (1.0-4.0)	-	
Cirrhosis	1	0.3	3.1 (1.1-8.7)	-	

-: p-value >0.15

* Likelihood ratio test (LR): p<.001; Hosmer-Lemeshow Goodness-of-fit test: p=0.65

† odds ratio's for the corresponding classified variable are given

‡ see methods section for corresponding ICD-9-CM codes

Mean age was 75 years (SD 8, range 65 to 110 years) and 38% were male. High-risk co-morbid conditions, e.g. cardiopulmonary disease, were present in 47% of subjects.

Table 2. Area under the receiver-operating-curve (AUC) and 95% confidence intervals (95% CI) of the clinical prediction rule in validation cohorts by year, immune status and region

Population	Year 1			Year 2		
	N	AUC	95% CI	N	AUC	95% CI
Non-immunized						
Region A	16,280	0.83	0.81-0.85	15,492	0.72	0.69-0.75
Region B	23,914	0.81	0.79-0.84	39,641	0.77	0.76-0.79
Region C	11,775	0.80	0.77-0.82	11,320	0.76	0.73-0.80
Overall	51,969	0.81	0.80-0.82	66,453	0.76	0.75-0.78
Immunized						
Region A	24,478	0.79	0.76-0.82	25,019	0.73	0.70-0.76
Region B	15,193	0.73	0.68-0.78	34,846	0.74	0.72-0.76
Region C	31,334	0.80	0.77-0.82	32,136	0.75	0.73-0.77
Overall	71,005	0.78	0.76-0.79	92,001	0.74	0.73-0.76

In gray-shade is the derivation cohort (n=16,280).

In univariate analysis, all potential predictors appeared more prevalent in subjects who were hospitalized or died and statistically significant associated with the combined end point, except for a history of immune-deficiency (see Table 1). In seniors with the end point, markedly higher prevalence of previous P&I hospitalization (16% versus 1%), pulmonary disease (40% versus 14%), dementia/stroke (31% versus 9%) and cancer (12% versus 2%) as compared to controls was observed.

Except for the co-morbid conditions diabetes, anemia, nutritional deficiencies, vasculitis/ rheumatological disorders, immune-deficiency and cirrhosis, all other variables independently contributed to the multivariable logistic regression model (table 1). In the modeling procedure, the presence of non-related diseases did not add to the limited prediction model including age, gender, previous P&I hospitalization and number of outpatient visits or predictive value was unacceptably low in the validation cohorts ($p>0.15$). After

Table 3. Prediction rule for estimating the probability of hospitalization for pneumonia and influenza and all-cause death

Characteristic		Score*
Age	<70	0
	70-74	+14
	75-79	+28
	80-89	+42
	>=90	+56
Female		+9
Outpatient visits in last year		
	0 visits	0
	1-6 visits	+11
	7-12 visits	+22
	>=13 visits	+33
Previous hospitalization for influenza or pneumonia		+63
Co-morbidity:		
	Lung disease	+18
	Heart disease	+6
	Renal disease or transplantation	+12
	Dementia or stroke	+22
	(Non-)haematological cancer	+48

* The sum-score for a given persons can be obtained by summing the scores for each applicable characteristic. The sum-score correlates with the predicted probability through the formula (see methods section).

including first-order interaction terms in the final model, six terms were statistically significant: gender×dementia/stroke, heart disease×cancer, age×heart disease, age×hospitalization, lung disease×hospitalization, dementia/stroke× hospitalization. Although it may be clinically plausible that risks of these combinations is more than the additive risks of each separate variable, we decided not to include them in the final prognostic model for three reasons: (1) these interactions were not observed in earlier studies, (2) they were not statistically significant in the other external cohorts and (3) they did not materially contribute to the discriminative value of the model. Performance of the final model was good (Goodness-of-fit test p=0.65). The model discriminated well between those with outcome (predicted probability 10%±1%) and those without outcome (0.2%±0.4%). The AUC was 0.83 (95%

Table 4. Test characteristics of sum-score cut-off points in derivation cohort (n=16,280)

Sum-score Category	No. (%)	OP (%)	RR	Cut-off point	PPV (%)	SE (%)	SP (%)	OM (%)	Selection (%)
≥0-<10	519 (3.2)	0.2	1.0	0	2.5	100	0	0	100
≥10-<20	1153 (7.1)	0.4	2.0	10	2.5	99.7	3.3	0.3	96.8
≥20-<30	2552 (15.7)	0.2	1.0	20	2.7	98.4	10.5	1.6	89.7
≥30-<40	2371 (14.6)	0.5	2.5	30	3.2	96.9	26.5	3.1	74.0
≥40-<50	1579 (9.7)	1.1	5.5	40	3.9	93.6	41.3	6.3	59.4
≥50-<60	2128 (13.1)	1.2	6.0	50	4.4	89.2	51.1	10.8	49.7
≥60-<70	1787 (11.0)	2.0	10.0	60	5.5	82.8	64.3	17.0	36.6
≥70-<80	1329 (8.2)	2.5	12.5	70	7.1	74.0	75.3	25.8	25.6
≥80-<90	938 (5.8)	4.2	21.0	80	9.2	65.7	83.5	34.1	17.4
≥90-<100	700 (4.3)	5.1	25.5	90	11.6	44.1	89.2	43.9	11.6
≥100	1224 (7.4)	15.4	77.0	100	15.4	46.9	93.4	52.9	7.4

OP: observed probability of outcome, RR: relative risk (<10 points is reference), PPV: positive predictive value, SE: sensitivity, SP: specificity, OM: outcomes missed

CI 0.81-0.85). AUC estimates were moderately lower, but acceptable across the validation cohorts (see table 2, range 0.72 to 0.81). The average discriminative power was approximately 0.05 points lower in the second as compared to the first season and 0.03 points lower in the immunized as compared to the non-immunized persons.

The prediction rule was derived from the final multivariate model in which a score was assigned to the presence or level of each variable (table 3). A sum-score for each patient, reflecting the probability of reaching an end point, was calculated by adding the scores of relevant characteristics. For instance, the sum-score for a 66-year old female patient with Hodgkin's disease who visited the outpatient clinic 7 times in the previous year and is recently diagnosed with asthma is 97 (9 + 48 + 22 +18) which is a 25.5 times higher risk than the lowest risk category (see also table 4).

The prediction rule can be used to identify those at highest risk for serious influenza associated complications and those therefore most likely to benefit from vaccination. Using the derivation cohort, for each cut-off level of the

Table 5. Practical implication of using a cut-off score (≥50) in validation cohorts by year, immunization status, and region. Percentages are given

Cohorts	Year 1					Year 2				
	OP	SE	OM	SP	RE	OP	SE	OM	SP	RE
Non-immunized										
Region A*	4.4	89	11	51	50	2.3	81	19	50	50
Region B	3.7	81	19	65	64	3.9	83	17	54	53
Region C	5.5	72	28	70	69	3.0	83	17	56	56
Overall	4.3	82	18	62	61	3.3	83	17	54	53
Immunized										
Region A	2.0	87	13	47	46	1.7	83	17	43	43
Region B	1.4	80	20	49	48	2.3	90	10	36	35
Region C	3.1	78	22	64	64	2.0	87	13	44	44
Overall	2.2	81	19	55	54	2.1	88	12	41	40

OP: observed probability, SE: sensitivity, OM: outcomes missed, SP: specificity, RE: reduction of the target population

* In gray-shade is the derivation cohort (n=16,280).

sum-score we calculated test characteristics (see table 4). A cut-off score of ≥50 had a sensitivity of 89% (1 out of 10 outcomes is missed) while the number of seniors selected would be halved. Patients with low risk assignment (score<50) had an observed average probability of 0.5%, those with high risk (≥50) had an average probability of 4.0%. With increasing cut-off level, the proportion of non-selected persons would increase, but the proportion of outcomes missed increases accordingly. Since the benefits of the cut-off value of ≥50 outweighed the risk of missing disease in the derivation cohort, we showed the practical consequences of this cut-off value in the different validation cohorts (table 5). On average, the sensitivity was high (82% to 83% in the non-immunized, 81% to 88% in the immunized) whereas the reductions of selected persons would range from 40% to 61%. When analyzing the test characteristics for both subsidiary end points separately, results were similar (not in table). Finally, influenza vaccination reduced any hospitalization or death by 43% (95% CI 39% to 47%) in persons with a score ≥50 and 33% (95% CI 24% to 45%) in those <50 points. The absolute reduction resulting from the vaccine in the high-risk segment of the population would be 16 per 1,000 vaccinated persons. In other words, only 67 persons have to be vaccinated to save one end point from happening.

Discussion

This study is unique in that we were able to derive and validate a prediction rule with acceptable reliability, discriminating ability and generalizibility using data on large-sized cohorts of seniors from three geographically disparate located health plans across the US. In comparison with previous prognostic studies,[7-10,22-26] our prediction rule has distinctive strengths. First, we developed a 9-factor prognostic scoring system in non-selected persons using information on predictors that can be readily assessed by both patients and health care providers at any time. Second, patients can be easily assigned to high or low risk category enabling providers to balance costs and benefits of health care. Third, the reliability, accuracy and generalizibility of the rule are supported by derivation in 16,280 seniors and validation in 11 large-sized external cohorts representing other areas across the United States, different epidemic season and immunization status.

The predictors incorporated in our prediction rule have been established in earlier epidemiological studies.[7-10,22-26] Age is a strong predictor for both respiratory infections, its main complication pneumonia and associated death.[27] Males also have been found to be at higher risk than females for influenza infections.[27] Patients with cardiac disease, especially congestive heart failure, are prone to exacerbations of underlying systemic disorders.[28] In addition, the disseminating potential of influenza infection in the lungs of patients with chronic respiratory disease is well known.[29] Patients with renal transplants[30] and cancer patients receive immune-suppressive medication which put them at risk for infections.[31] Also, previous hospitalization for pneumonia or influenza has been reported previously as a risk factor.[32] Relatively little is known, however, about the risk of elderly with dementia or stroke. Our results indicate that there is substantial risk for these persons of dying or being hospitalized during an influenza epidemic.

Diabetes was not independently associated with a higher risk of P&I hospitalization or death in both derivation and validation cohorts. In the modeling procedure, similar information needed for risk assessment was acquired through other predictors as age, gender and previous health care use. It appeared that two-thirds of diabetics had a score ≥50 points and therefore the disease may be seen as an indicator for high influenza risk which is in accordance with other studies.[33]

To our knowledge, this is the first study to demonstrate that risks are not materially modified by changing epidemics or immunization status. We believe

therefore that results are applicable to future epidemic seasons. Furthermore, our prediction rule may be used in non-vaccinated persons, especially those who have high scores, to efficiently target them for influenza vaccination and other appropriate medical care whereas in vaccinated persons with high scores, risk assignment based on the rule help practitioners direct medical care and for those with low scores avoid unnecessary additional diagnostic, therapeutic or preventive measures.

A score ≥50 points represented a high risk with an average expecting occurrence rate of P&I hospitalization or mortality of 4%. In the derivation cohort, relatively lower numbers of persons were observed with higher cut-off values while the numbers of outcomes missed increased substantially. Although we acknowledge that the proportion of outcomes missed decreases with a lower cut-off score, we feel that using the cut-off level of 50 points was acceptable in all validation cohorts whereas the numbers to select for care were reduced to between 40% and 60% on average. From the scoring formula some patient profiles with high risk can easily be identified on the basis of routine clinical information: e.g. everyone who has had a previous hospitalization for pneumonia or influenza or a history of cancer and who is aged over 90 years, and all elderly aged over 80 years with at least one of the high-risk co-morbid conditions. Since we demonstrated that influenza vaccination reduced P&I hospitalization or death by 43 percent in persons with a score ≥50 points, no opportunities should be missed to vaccinate these persons against influenza and pneumonia.

For the development of the clinical prediction rule, we studied only persons aged 65 years and older. The majority of excess deaths and many, if not most, of the excess hospitalizations for influenza associated complications occur in this group. However, for many years, persons with high-risk conditions under age 65 have also been included among the high risk groups targeted for vaccination, and for the 2000-2001 season, the ACIP lowered its age-based recommendations for annual vaccination down to 50 years.[34] How our prediction rule might apply to these other high-risk groups remains to be seen.

We used pneumonia and influenza hospitalizations and deaths from all causes as the end points for the prediction rule. These outcomes are highly correlated and have traditionally been among the main measures used to assess and define the magnitude and impact of influenza epidemics.[1] However, influenza may also be responsible for a wide range of other complications including exacerbations of underlying medical conditions leading to increased outpatient and inpatient health care use.[11] It is not clear how the results of our model might apply to these other outcomes.

In conclusion, we derived and validated a prediction rule for quantifying the probability of P&I hospitalization or death with acceptable reliability, discriminating ability and generalizibility. In addition to the recommendation to routinely immunize all persons over 50 years of age against influenza, our prediction rule may help practitioners to target efficiently additional efforts to those who need preventive and therapeutic measures most.

Acknowledgment

We kindly acknowledge the funding of this project through the American Association of Health Plans by the Centers for Disease Control and Prevention. Mr. Hak's participation was supported by a grant from the Dutch Asthma Foundation, Leusden, the Netherlands.

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CHAPTER 4

Confounding by indication in non-experimental evaluation of vaccine effectiveness: the example of influenza vaccination

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Confounding by indication in non-experimental evaluation of vaccine effectiveness: the example of influenza vaccination

Randomized allocation of vaccine or placebo is the preferred method to assess the effects of the vaccine on clinical outcomes relevant to the individual patient. In the absence of phase 3 trials using clinical endpoints, alternative non-experimental designs to evaluate vaccine effects or safety are often used. The application of these latter designs may, however, lead to invalid estimates of vaccine effectiveness or safety. Since patients with poor prognosis are more likely to be immunized, selection for vaccination is confounded by patient factors that are also related to clinical endpoints. This paper describes several design and analytical methods aimed at limiting or preventing this confounding by indication in non-experimental studies. In short, comparison of study groups with similar prognosis, restriction of the study population and statistical adjustment for dissimilarities in prognosis are important tools and should be considered. Only if the investigator is able to show that confounding by indication is sufficiently controlled for, results of a non-experimental study may be of use to direct an evidence-based vaccine policy.

Key-words: influenza, vaccine, effectiveness, confounding, methods, observational studies

Submitted as: Hak E, Verheij ThJM, Grobbee DE, Nichol KL, Hoes AW. Confounding by indication in non-experimental evaluation of vaccine effectiveness: the example of influenza vaccination.

The health economic impact of influenza epidemics is considerable.[1-3] In most western countries, the use of inactivated influenza vaccines by vulnerable patient groups is advocated to prevent complications.[4] However, uptake of the vaccine remains low, especially in those who need it most.[4-6] Disbelief in the vaccine 's effects on clinical outcomes relevant to the individual patient may be one of the major reasons for disappointing immunization rates.[3,4,6-8]

Effectiveness of influenza vaccination: randomized controlled trials

The clinical effects of influenza vaccines such as reduction of major symptomatic events or death should preferably be studied in phase 3 randomized controlled trials (RCT).[9] Provided that the sample size is large enough, randomized assignment of patients to vaccine or placebo enables valid assessment of vaccine effects through comparing the occurrence of outcomes in both patient groups with similar prognosis. Such trials can be conducted among various segments of the patient population and may give insight into positive as well as negative clinical consequences of immunization in daily practice. Results of large enough trials in which the primary endpoint is a clinical outcome rather than a surrogate endpoint (e.g. immune response) provide

crucial information on the true impact of these preventive measures and are best suited to guide health care decisions.[10,11]

However, scientists face many obstacles when planning a RCT for clinical evaluation of influenza vaccines. First and foremost, as the incidence of influenza-related complications or adverse effects is low these trials would entail great expense because large numbers of patients are required.[1,12] Second, several influenza seasons may need to be observed as the virulence of circulating influenza viral types is highly variable and unpredictable.[1,6,13] Finally, once the vaccine has been licensed ethical concerns may be raised to further evaluate its effectiveness in placebo-controlled studies, especially when persons at high risk for complications are involved. Because of these limitations, post-licensing or phase 4 studies evaluating the vaccine's clinical effectiveness or safety usually use a non-experimental approach, notably a case-control or cohort design.[9] The vaccine's effectiveness is interpreted as the percentage reduction in risk of influenza-associated complications attributable to vaccination, given in percent by 1-RR in cohort studies or 1-OR in case-control studies.[3] The main difference between experimental and non-experimental designs lies in the absence of random allocation of the intervention, e.g. vaccination, by the investigator.

Effectiveness of influenza vaccination: non-experimental studies

One of the major problems encountered in non-experimental evaluation of intended drug effects is the 'natural' presence of incomparability of prognosis among subjects receiving the drug and those who do not.[14] In non-experimental influenza vaccine studies, the vaccine group typically comprises patients with more severe disease or (perceived) higher risk, either as a result of self-selection or physician preference, than the non-vaccinated (control) group.[15,16] In contrast, those with a contra-indication for the intervention will usually be found in the control group only. Thus, selection of exposure is confounded with patient factors, both clinical and non-clinical, that are also related to (detection of) the outcome. This phenomenon may equally apply to qualitative (absence/presence) as well as quantitative (dosing schedule) aspects of exposure and is usually referred to as 'confounding by (contra-)indication' or 'channeling'.[14,17,18] Crude, unadjusted, results of non-experiments may therefore lead to invalid inference regarding influenza vaccine effectiveness and potential side effects, i.e. underestimation of both beneficial and adverse effects in most circumstances. The obligation of the investigator is to design and analyze the study in such a way that reduction or removal of this type of bias can be achieved.

Prevention of confounding by indication: study design issues

Preventing or limiting confounding by indication can be achieved in the design and data-analytic phase of case-control and cohort studies (see also Table 1). In designing a non-experimental study of vaccine effectiveness, valid inferences on preventive effects can be drawn in those situations in which patient groups are compared who have similar indications but have undergone different interventions. These designs could be viewed as 'natural experiments'. Hypothetically, patients receiving the influenza vaccine because their general practitioner (GP) believes in it and is able to organize the intervention program (intervention group) could be compared with a group of patients listed with a GP who does not immunize his patients against influenza (control group). Such comparison groups may however be difficult to identify in one health care system. Another, less preferred, design option constitutes an ecological study in which vaccine effects among patients residing in different areas are compared. Similarity of ecological comparison groups highly depends on distribution of patient characteristics in different areas. In this respect, a design in which the incidence of influenza-associated complications of a historical control group of patients before the introduction of the influenza vaccine is compared with the incidence of such complications in patients after its introduction (intervention group) in one area may be a better option. Such a design, however, risks the incomparability of influenza seasons.

Table 1. Methods to reduce confounding by indication

Design methods
• Comparison of groups with similar prognosis (e.g. 'natural experiment' or use of historical controls)
• Restriction or stratification of study population (e.g. age-strata, gender, current/inactive disease)
• Individual matching of exposed and non-exposed into main prognostic strata ('quasi-experiment')
Statistical methods
• Statistical control of confounding factors in multivariable regression model
• Subclassification of patients on levels of the propensity score
• Pseudo-randomization on levels of instrumental variables

Alternatively, the study domain could be restricted to patients with a more or less similar prognosis such as institutionalized elderly patients.[19] Strict admission criteria could however limit the generalizibility and applicability of results to other segments of the population, while incomparability of comparison groups and residual confounding may persist. Stratification of the study population on levels of important confounding variables, like for example age, and within stratum comparisons also enhances internal validity.[20]

Another option consists of individual pair-matching of vaccinated and non-vaccinated subjects within strata of important prognostic variables sometimes referred as 'quasi-experiment'. This technique was used in a non-experimental evaluation of the effects of placement of ventilation tubes and proved to reduce confounding bias.[21] The design of a quasi-experiment is, however, costly as it requires sufficiently large numbers of patients within each stratum. Except for restriction and stratification, to our knowledge none of the other design options mentioned above has been applied in non-experimental evaluation of currently used influenza vaccines.

Prevention of confounding by indication: data analytical issues

Independent of the study design, statistical adjustment for dissimilarities in prognostic factors between the patient groups receiving and not receiving the vaccine can be applied to enhance validity.[1,3,22-24] A prerequisite is that valid and precise data are obtained through the design used to estimate the patient's prognosis without too many missing data. In other words, to optimize statistical adjustment, the prognosis of each patient should be measured by as many valid indicators as possible to allow adjustments afterwards. In primary care, for example, the presence of current disease as indicated by presence of GP consultations in the year preceding the study, also referred as 'active patient', is essential to allow valid adjustment of potential confounding. In the ideal situation in which all prognostic patient features can be measured, the exact degree of bias can be quantified and used to draw valid conclusions from the data. In practice, this is usually impossible due to cost restrictions and difficulty, and in that case residual confounding or hidden bias can not be ruled out. However, although in many non-experimental studies residual confounding may be present, it can be shown that there are limits to the extent of mathematical explanation by this unmeasured confounding. Its putative effects mainly depend on the expected prevalence of the unobserved variable(s), and its associations with vaccination and outcome. Investigators should therefore always reflect on the potential magnitude of the impact of such bias on the effectiveness estimate for example by using sensitivity analysis.[16,26]

In general, three main methods for statistical adjustments can be applied: (1) statistical control of confounding variables in a multivariable regression model;[14,18] (2) sub-classifying or matching patients on levels of a so-called 'propensity score' [16,25-27] and (3) the use of an instrumental variable to enable statistical pseudo randomization and to account for any residual confounding.[28]

The first option is commonly used and comprises several steps: identification of confounders in the data-set, univariate stratification of exposure groups on levels of the confounder to estimate the vaccine effectiveness estimate adjusted for this single variable (e.g. age) and multivariable control including confounding variables that collectively influence the estimated relationship between exposure and outcome in the modeling procedure.

A method to optimize statistical adjustment for confounding by indication in non-experimental studies, notably when the number of prognostic variables is large, has been proposed by Rubin and Rosenbaum. They introduced the 'propensity score' method.[16,25-27] This score is the conditional probability of exposure to a treatment given a set of observed variables that may influence the decision to vaccinate. The propensity score can be derived from a multivariable logistic regression analysis in which those variables that are statistically significant associated with exposure (e.g. vaccination) are included. Obviously, the outcome variable should not be included as a co-variate. A higher score indicates a higher probability of receiving the vaccine. Sub-classification of subjects on levels of this single variable or including this variable as a single co-variate in a multivariable regression model tends to balance all of the observed variables, but not the unobserved.[16,25,27] The use of this score and matched sampling will also implicitly incorporate any interactions among confounders. Thus, this technique enables the investigator to assess the association of vaccination with specific outcomes in patients with a more or less equal probability of receiving the vaccine. Discriminant matching for multivariate normal co-variates as described by Cochran[29] and the use of a 'confounder score' as proposed by Miettinen are related techniques.[30]

To overcome the potential lack of balance on unobserved prognostic indicators (e.g. health behavior), the instrumental variable method has been suggested. This technique originates from the field of econometrics and has so far not been extensively used in medical research. In short, patients are subdivided according to levels of a co-variate that is associated with the exposure, but not associated with the outcome. This pseudo-randomization may lead to equal distribution of health characteristics in both non-exposed and exposed people and thus prevent potential confounding. For example, McClellan et al. calculated the

distance to the hospital on the basis of zip-codes and divided patients into those living within a small area around the hospital and those outside that area in a study on cardiovascular procedures.[28] Distance to the hospital did fulfill the criteria for instrumental variables. Heart catheterization was more prevalent in the inner circle than the outer circle, and mortality rates were similar. This was in contrast with their prior finding using conventional control for confounding in which mortality rates appeared higher in patients who underwent the surgical procedure. Since the validity of this latter method should be evaluated in other medical studies and instrumental variables may be hard to identify, we will not further elaborate on this statistical procedure.

The presence of confounding by indication in non-experimental evaluation of influenza vaccination and some of the above-mentioned tools to reduce its impact are discussed in more detail on the basis of data derived from a recent study by our group.

An example: Influenza vaccine effectiveness in adult patients with pulmonary disease

We examined the effect of influenza vaccine on the incidence of influenza-associated complications in 1,696 adult patients with chronic obstructive pulmonary disease (COPD) or asthma during the 1995/96 influenza A epidemic.[31] The study was a one-season prospective cohort study using the medical database of the Utrecht General Practitioners Network. GP patient records were reviewed for all study subjects. As a first design approach to limit confounding by indication, vaccinated and non-vaccinated patients with pulmonary disease were compared rather than vaccinated patients and controls from the community. The study population was restricted to those with an indication for vaccination according to the guidelines of the Dutch Health Council. In table 2 we give crude and adjusted effectiveness estimates using the conventional control of confounding by multivariable logistic regression analysis. In spite of restriction of the study population, crude results appear to suggest that the vaccine is ineffective and may even lead to complications (odds ratio (OR) 1.14). However, further statistical adjustments notably for age, disease and GP visits resulted in striking changes of the effectiveness estimate to a relative risk of 0.76 suggesting an overall vaccine effectiveness of 24 percent in this population —a relative parameter change of 33 percent. Addition of other co-variates in the final model did not substantially change the vaccine effectiveness estimate.

Table 2. Crude and adjusted odds ratio's for an acute episode of low respiratory tract or cardiac disease or death during an influenza epidemic in vaccinees and non-vaccinees

Study population and analysis	Adjusted for:	Odds ratio (95% CI)
Adult patients (18-102 y, n=1696) Conventional control: MLR*	Crude value:	1.14 (0.84-1.55)
	+ age (in years)	0.87 (0.64-1.20)
	+ disease (asthma/COPD)	0.82 (0.59-1.13)
	+ GP visits (in number)	0.76 (0.54-1.05)
	+ remaining factors	0.76 (0.54-1.06)
Elderly patients (65-102 y, n=630) Conventional control: MLR*	Crude value:	0.57 (0.35-0.93)
	+ age (in years)	0.56 (0.35-0.92)
	+ disease (asthma/COPD)	0.53 (0.32-0.87)
	+ GP visits (in number)	0.50 (0.30-0.83)
	+ remaining factors	0.50 (0.29-0.83)
Younger patients (18-64 y, n=1066) Conventional control: MLR*	Crude value:	1.27 (0.84-1.94)
	+ age (in years)	1.11 (0.73-1.70)
	+ disease (asthma/COPD)	1.08 (0.70-1.66)
	+ GP visits (in number)	0.94 (0.61-1.47)
	+ remaining factors	0.94 (0.60-1.45)
Quasi-experiment (18-64 y, n=676) Conventional control: MCLR**	Matched crude value:	0.90 (0.53-1.52)
	+ age/ disease/GP visits/ remaining factors	0.89 (0.52-1.54)
Younger patients (18-64 y, n=1066) Propensity score + MCLR**	Matched crude value:	0.87 (0.56-1.35)
	+ age/ disease/GP visits/ remaining factors	0.86 (0.55-1.35)

* MLR: Multivariable logistic regression analysis;
** MCLR: Multivariable conditional logistic regression

Most probably the adjustments were still incomplete. More precise measurements of disease severity such as pulmonary function, atopy or hyper-reactivity were not available. Therefore, a second approach to limit confounding consisted of subdividing the whole study population into two age-strata (≥65 years, 18-64 years) in which prognosis of vaccinees and non-vaccinees within each age-stratum is less deviant (see also table 2). Apart from issues of modification of the effects of the vaccine by age, which is beyond the scope of this article, with this approach, statistical adjustments for the same confounding factors resulted in smaller relative parameter changes of 12 and 26 percent, respectively, in both age-categories. This suggests that stratification or age-restriction may further reduce residual confounding. Still, inferences on the two age subgroups should be made with caution. In the elderly, a substantial and statistically significant reduction in the outcome rate was observed even without controlling for confounding (OR 0.57, 95% confidence interval [CI] 0.35-0.93). Addition of prognostic factors into the multivariate model led to a further increase in the estimate of vaccine effectiveness indicating some residual confounding after stratification. However, in the working-age adults the crude odds ratio was well above 1.0 and despite adjustment for the available prognostic indicators we could not demonstrate a significant reduction (OR 0.94, 95% CI 0.60-1.45). This suggests that results of restricted populations are not necessarily applicable to other segments, in this case younger patients. Because Neuzil and colleagues showed considerable impact of influenza in a younger group of women[6] and we have shown that in the Netherlands the current influenza target group comprises at least 40 percent of high-risk persons under 65 years of age,[32] we further examined potential confounding in this particular age-group.

As a third approach to limit potential confounding by indication in the original design, we used the data of this younger age group (18-64 years) in a 'quasi-experiment'. First, we identified the three main prognostic factors: age (5-years age-category), underlying pulmonary disease (asthma or COPD) and GP visiting rate (0, 1-2, and ≥3 visits). Next, we classified each subject, vaccinated or non-vaccinated, into one of the 54 combinations of these factors. Within each stratum we then randomly sampled from either the vaccinated or the non-vaccinated group as many patients as were available in the comparison group with the lowest number of subjects. For example, if 5 vaccinated and 2 non-vaccinated patients were between 20 and 24 years old, had asthma and consulted the GP 5 times in the preceding year, we sampled 2 patients at random from the exposed group to form a stratum matched group. In all, 390 patients (37%) were excluded from the original study population (n=1066) and 676 patients were available for the quasi-experiment. After this matching

procedure it appeared that the vaccine reduced the occurrence of outcomes by 11 percent, after adjustments for the main confounders and remaining covariates (i.e. health insurance, gender), but the estimate was not statistically significant (see table 2). Only minor changes were observed after statistical adjustment, suggesting that confounding by differences in the known prognostic factors was largely removed. A major limitation may prohibit the use of the above-mentioned 'quasi experiment'. Pair-matching is time-consuming and can considerably reduce the power of the study as numbers of matched patients in separate strata become small. In our example 37% of the initial study population had to be excluded. To avoid these issues, we finally applied analytical control of confounding by using the 'propensity score'.

In our example, we used the 1066 patients aged between 18 and 64 years to calculate the probability score of being vaccinated. Our final multivariable logistic regression model with the dependent variable vaccination included age, underlying disease, number of GP visits, gender and health insurance. We then categorized the propensity score into quintiles and matched vaccinees and non-vaccinees on levels of the probability to be vaccinated. In the multivariable conditional logistic regression analysis we matched on the categorized levels of the score and calculated crude and adjusted odds ratio's of vaccination for the outcome. The overall adjusted odds ratio of 0.86 appears to suggest a 14% reduction of complications resulting from the vaccine. The finding of the 'quasi-experiment' in which stratum-matched pairs of vaccinees and non-vaccinees were compared was validated by this statistical method. As was expected, 95% confidence intervals were smaller, but point estimates were nearly the same. The latter techniques changed the effectiveness estimate from a crude estimate of –27% in the original design to 11% and 14% using the 'quasi-experiment' and 'propensity score', respectively; relative parameter changes of more than 30%. In addition, the propensity score method resulted in slightly smaller 95% confidence intervals than the conventional adjustment. Although our study lacked adequate power to demonstrate a statistically significant reduction of outcomes resulting from the vaccine, the adjusted effectiveness point estimates are compatible with a statistically significant 11% reduction of outpatient visits for respiratory disease in elderly lung patients as observed by Nichol and colleagues.[33]

Conclusion

Randomized allocation of vaccine or placebo is the preferred method to assess the effects of the vaccine on clinical outcomes relevant to the individual patient. In the absence of phase 3 trials using clinical endpoints, alternative non-experimental designs to evaluate vaccine effects or safety are often used. The application of these latter designs may, however, lead to invalid estimates of vaccine effectiveness or safety. Since patients with poor prognosis are more likely to be immunized, selection for vaccination is confounded by patient factors that are also related to clinical endpoints. This paper describes several design and analytical methods aimed at limiting or preventing this confounding by indication in non-experimental studies. In short, comparison of study groups with similar prognosis, restriction of the study population and statistical adjustment for dissimilarities in prognosis are important tools and should be considered. Only if the investigator is able to show that confounding by indication is sufficiently controlled for, results of a non-experimental study may be of use to direct an evidence-based vaccine policy.

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CHAPTER 5

Clinical effectiveness of conventional influenza vaccination in asthmatic children

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Clinical effectiveness of conventional influenza vaccination in asthmatic children

Background Influenza immunization rates among young asthmatics remain unsatisfactory due to persistent concern about the impact of influenza and the benefits of the vaccine. We assessed the effectiveness of the conventional inactivated trivalent sub-unit influenza vaccine in reducing acute respiratory disease in asthmatic children.

Subjects and Methods We conducted a two-season retrospective cohort study covering the 1995-96 and 1996-97 influenza A outbreaks in twenty-two computerized primary care practices in the Netherlands. 349 patients aged between 0 and 12 years meeting clinical asthma-criteria were included. 14 children were lost to follow-up in the second season. The occurrence of physician-diagnosed acute respiratory disease episodes including influenza-like illness, pneumonia, bronchitis/-iolitis, asthma exacerbation and acute otitis media in vaccinated and unvaccinated children were compared after adjustments for age, prior health care and medication use.

Results The occurrence of acute respiratory disease in unvaccinated children was 28% and 24% in the 1995-96 and 1996-97 season, respectively, and was highest in children <6 years (43%). The overall pooled clinical vaccine effectiveness was 27% (95% confidence interval [95% CI] -7% to 51%, p=0.11) after adjustments. A statistically higher vaccine protectiveness of 55% (95% CI 20% to 75%, p=0.01) was observed among asthmatics <6 years compared with those ≥6 years of age: -5% (95% CI –81% to 39%, p=0.85).

Conclusion The occurrence of acute respiratory disease among asthmatic children during influenza epidemics is very high, notably in the youngest. Influenza vaccination can substantially reduce morbidity in asthmatic infants and preschool children. Larger, preferably experimental, studies are needed to establish whether older asthmatic children benefit from the vaccination as well.

Key words: influenza, vaccination, prevention, general practice, child, asthma

Submitted as: Smits AJ, Hak E, Stalman WAB, Essen GA van, Hoes AW, Verheij ThJM. Clinical effectiveness of conventional influenza vaccination in asthmatic children.

Asthma is one of the commonest chronic conditions in childhood with a prevalence of approximately 7%.[1] An important causal agent in asthma exacerbations is influenza, especially during epidemics.[2,3] Influenza has a major impact on children's well-being and need for medical treatment[4-6] and predisposes to complications such as pneumonia[7] and acute otitis media.[7-10] Annual influenza vaccination is therefore recommended worldwide for this population at risk.[11]

Despite this recommendation, the low costs of the vaccine and the absence of systemic side-effects,[2,12] immunization rates remain low.[11] This seems mainly

attributable to both the physician's and patient's doubt about the clinical protectiveness of the vaccine.[13,14] So far, only indirect protectiveness against serologically proven influenza infection has been demonstrated in children (42 to 95% relative risk reduction).[8,15] Furthermore, only few studies provide some evidence of a reduction in acute otitis media rates and febrile illness episodes following influenza vaccination.[8-10,15] The vaccine's clinical protectiveness against acute respiratory disease (including influenza-like illness, pneumonia, bronchitis/-iolitis, asthma exacerbation and acute otitis media) in asthmatic children has not been demonstrated.[2,16,17] We therefore evaluated, in a primary care-based, two-season study, whether influenza vaccination is effective in reducing the occurrence of acute respiratory disease in asthmatic children. In addition, we assessed whether the impact of influenza-associated morbidity and the effectiveness of influenza vaccination are different in infants and preschoolers as compared with schoolchildren.

Methods

Design

Our study was designed as a retrospective cohort study. We defined a cohort of young asthmatics originating from a primary care database in 1995. This cohort was followed up during two consecutive years and influenza seasons (1995-96 and 1996-97).

Setting

Twenty-two general practitioners in five primary care centers participated in the study. The practices cover a representative sample of approximately 40,000 patients. Practices are member of the Utrecht University General Practice Network[18] and are situated in urban as well as rural areas in the central part of the Netherlands. All physicians used computerized medical records to register patient contacts. Diagnoses were coded according to the International Classification of Primary Care (ICHPPC-2) and therapeutic agents according to the Anatomical Therapeutic Classification (ATC).[19-21] All physicians regularly received extensive training in uniform registration of respiratory tract diseases. Anonymous use of patient information for scientific research derived from the database has been approved by the medical ethical committee of the University Medical Center Utrecht.

Subjects

First, a pre-selection of potential study subjects was performed using a 'computerized influenza prevention module'.[22] In short, this module identified patients in high-risk categories for influenza infection on the basis of disease tags, ICPC- and ATC-codes. Next, potential study subjects were selected by their physicians on the basis of asthma criteria defined in the guidelines of the Dutch College of General Practitioners.[23]

These criteria state that in a patient under six years of age (probable) asthma is a clinical diagnosis based on symptoms and signs only. Required criteria are: recurrent episodes of coughing and/or congestion (> 5 times a year, > 10 days an episode) or wheezing associated with a viral infection and one of the following:

- improvement of complaints following a bronchodilator or
- indications of allergic stimuli causing airway symptoms or
- constitutional eczema or
- increase of wheezing and/or dyspnoea with age or
- asthma, hay-fever or eczema in a first-degree sibling.

Between six and twelve years, the same criteria are required in addition to pulmonary function measurements. Asthma is confirmed when forced expiratory volume or peak flow measurement indicates a reversible bronchial obstruction and/or when day-night variability (amplitude/mean >31%) is present.

We admitted 370 young asthmatics aged 0-12 years meeting above-mentioned criteria in November 1995. To ensure current asthma activity, we excluded 21 children that did not contact their physician in the year preceding the inclusion date. Fourteen subjects were lost to follow-up in the second season and consequently excluded in the 1996-97 season

Intervention

Influenza vaccination was offered to patients in accordance with guidelines of the Dutch College of General Practitioners.[24] Annually, the parents of indicated patients received a personal postal invitation. Mass vaccination of compliers with the invitation for influenza vaccination took place each year in the first two weeks of November. Children under six years of age received another dose four weeks after the first, if they had not received a vaccine in prior years. Each year the trivalent subunit vaccine was composed of strains recommended by the World Health Organization.

Influenza seasons

Influenza monitoring was performed by the Dutch National Influenza Center in collaboration with the Dutch Sentinel Practice Network.[25,26] We defined influenza seasons as the period in which the incidence of influenza-like-illness reported by the sentinel practices was above four per 10,000 inhabitants per week. The first season started in week 46 (1995) and ended in week 10 (1996). Peak incidence reached 39 per 10,000 inhabitants per week. Although there was good matching between the vaccine and the predominant influenza strain in this season, circulating viruses were antigenic similar to those in the preceding two seasons (1992-93 and 1993-94). The second season started in week 48 (1996) and ended in week 11 (1997). Its peak incidence reached 29 per 10,000 inhabitants per week. Due to antigenic drift this season's predominant strain was substantially different from earlier years. The Sydney-type strain, however, appeared to be well covered by that year's vaccine.

Data collection

All data were extracted anonymously from electronic patient records and classified by a physician (AJS). At the inclusion date general demographic characteristics such as sex, year of birth, region and health insurance were registered. The following prognostic indicators were determined in the 12 months prior to vaccination for every season: number of physician contacts, number of contacts associated with lower airway complaints, number of referrals (pediatrician, pulmonologist or ear, nose and throat-physician), antibiotic prescriptions, use of bronchodilators, antihistamines, cromoglicates, inhalation and oral corticosteroids and atopy. Each year vaccination status was assessed by search in free text and/or ICPC-code R44.1.

Outcome measures

Our combined outcome measure was the occurrence of one or more episodes of acute respiratory tract disease defined as physician-diagnosed influenza-like illness, pneumonia, bronchitis/-iolitis, asthma exacerbation or acute otitis media during the influenza seasons. All episodes were confirmed in free text and/or by ICPC-codes (R02-R05, R25, R29, R78, R80, R81, R83, R91, R96, R99, or H71).

Statistical analysis

With EPI-Info, version 6 (CDC, Atlanta, Georgia, USA) we estimated that a minimal cohort size of 330 children would give us a 80% chance of detecting a reduction of at least 50% in outcome events among recipients of the vaccine.[15,27,28] We assumed for this calculation an immunization rate of 45%, an event rate of 25% in unvaccinated persons and a two-sided alfa level of 5%.

Statistical analysis was performed using SPSS for Windows, version 8.0 (SPSS Inc., Chicago, Illinois, USA). We dichotomized age into <6 and ≥6 years. This cut-off was chosen because of differences in clinical diagnosis of asthma and hypothesized differences in risk for complications of influenza between age groups. All analyses were performed for the two influenza seasons separately and for both seasons combined.

Uni- and multivariable logistic regression modeling was used to obtain crude and adjusted odds ratios and their 95% confidence intervals (CI) of vaccine effectiveness. In the first stage of constructing the multivariate model we defined vaccination status as the exposure term and acute respiratory disease as the dependent variable. We then added each potentially confounding variable independently to the model to assess its effect on the estimated vaccine effectiveness. In the final model we only included those variables that materially altered the effect estimate of influenza vaccine exposure. This model was used to obtain adjusted odds ratios in the complete cohort as well as in subgroups. Effect modification by age category and season was statistically tested by adding this variable and its first-order interaction term to the final model. Also, we applied subgroup analysis. We used the adjusted odds ratios as an approximation of the relative risk and calculated the adjusted effectiveness as follows: (1-adjusted odds ratio)*100%. We used mixed effects regression modeling with MIXOR, version 2 (D. Hedeker, RD Gibbons, Illinois, Chicago, USA) to take into account a possible child effect in the pooled analysis.[29] Point estimates and standard errors did not change substantially compared with the conventional logistic regression modeling.

Results

Vaccination rates increased from 41% in the first season to 45% in the second (see Table 1). Vaccinees were more likely to be girls, older, have a higher medical consumption (in primary as well as in secondary care) and use more pulmonary medication (any of four types) and prednisone than non-vaccinees.

Attack rates of acute respiratory disease in non-vaccinees, were 28% in the 1995-96 and 24% in the 1996-97 season, respectively, and 26% overall (see Table 2). Acute respiratory disease was much more common among unvaccinated children under 6 years (43%) than among those 6 years or older (15%).

Table 1. Seasonal baseline characteristics*

Characteristic	1995/96 season (n=349)		1996/97 season (n=335)		Both seasons (n=684)	
	Vac + (n=144)	Vac- (n=205)	Vac+ (n=149)	Vac- (n=186)	Vac+ (n=293)	Vac- (n=391)
Male sex	55	66	54	69	55	67
Age, mean (SD), y	6.6 (3.1)	6.0 (3.3)	7.7 (3.1)	7.0 (3.2)	7.1 (3.1)	6.5 (3.3)
GP visits, mean (SD), no.	7.1 (5.9)	6.1 (4.9)	6.5 (5.0)	4.2 (4.2)	6.8 (5.4)	5.2 (4.6)
Specialist visits, mean (SD), no.	0.3 (0.7)	0.2 (0.4)	0.3 (0.6)	0.1 (0.5)	0.3 (0.6)	0.2 (0.5)
Pulmonary medication use	84	76	77	56	80	67
Oral prednisone use	5	1	3	3	4	2

* Data are presented as percentages except where noted otherwise.

In multivariate modeling the child's age, number of physician contacts, number of referrals, use of pulmonary medication and use of oral prednisone in the year preceding baseline confounded the association between vaccination status and the outcome and were therefore included in the final model. Although the point estimates of vaccine effectiveness differed substantially among the two seasons, differences were not statistically significant (p>0.10). Overall, the influenza vaccination was associated with a 27% reduction in the occurrence of acute respiratory disease (95% CI: -7% to 51%, p=0.11, Table 2). We recorded a statistically significant reduction of acute respiratory disease of 56% (CI: 18% to 76%, p=0.01) in the 1996-97 season only.

Overall, a statistically significant higher protectiveness (p=0.02 for interaction) was observed in children <6 years of 55% (CI: 20%, 75%, p=0.01) than in those ≥6 years: -5% (CI: -81%, 39%, p=0.85). In children under 6 years of age, the vaccine was associated with a 32% reduction (95% CI −39% to 67%) in the outcome in the 1995-96 season and a 77% (95% CI 35% to 92%) reduction of outcomes in the 1996-97 season.

Table 2. Attack rates of acute respiratory disease, crude and adjusted effectiveness by season and age category

	Attack rate in Non-Vaccinees No. (%)	Attack rate in Vaccinees No. (%)	Crude effectiveness % (95% CI)	Adjusted effectiveness* % (95% CI)	p-value
Both seasons					
All children	102 (26.1)	63 (21.5)	22 (-11, 46)	27 (-7, 51)	0.11
0 to 5 years vac-: 157 vac+: 98	68 (43.3)	28 (28.6)	48 (10, 70)	55 (20, 75)	0.01
6 to 13 years vac-: 234 vac+: 195	34 (14.5)	35 (17.9)	-29 (-115, 23)	-5 (-81, 39)	0.85
1995/96 season					
All children	57 (27.8)	40 (27.8)	0 (-61, 38)	-1 (-68, 39)	0.97
0 to 5 years vac-: 94 vac+: 58	41 (43.6)	21 (36.2)	27 (-44, 63)	32 (-39, 67)	0.29
6 to 13 years vac-: 111 vac+: 86	16 (14.4)	19 (22.1)	-68 (-251, 19)	-52 (-225, 29)	0.28
1996/97 season					
All children	45 (24.2)	23 (15.4)	43 (0, 77)	56 (18 , 76)	0.01
0 to 5 years vac-: 63 vac+: 40	27 (42.9)	7 (17.5)	72 (26, 89)	77 (35, 92)	0.01
6 to 13 years vac-: 123 vac+: 109	18 (14.6)	16 (14.7)	0 (-108, 52)	31 (-54, 69)	0.37

* adjusted effectiveness = (1- adjusted OR) * 100%

Discussion

Our study demonstrates that children with asthma suffer substantially from influenza-associated morbidity. Almost a quarter of these children visited the primary care physician during the influenza epidemics. Importantly, medically attended acute respiratory disease occurred in 4 out of 10 infants and preschoolers with asthma. Our data further suggest that the conventional influenza vaccine can substantially reduce the occurrence of acute respiratory disease in this young high-risk group during influenza epidemics. Age seems therefore more important than the certainty or severity of the asthma-diagnosis.

To appreciate these findings, some potential limitations of our study need to be addressed. The size of the cohort was large enough to demonstrate an expected 50% reduction of outcomes resulting from the vaccine based on earlier observations. Sugaya et al.[15], for example, recorded a 49% reduction in febrile episodes in vaccinated asthmatic children aged 2 to 14 years, Khan et al.[28] demonstrated a vaccine efficacy for preventing school absenteeism due to respiratory illness of 56% in healthy children and Gross et al.[27] recorded a 50% reduction in influenza-related illness among the elderly in a large meta-analysis. In the 1996-97 season we were therefore able to demonstrate a statistically significant vaccine protectiveness of 56% overall and of 77% in the youngest asthmatics. However, vaccine protectiveness seemed less in the first season (-1 percent). Although in that season a protectiveness of 32% was observed in the younger children, overall no protectiveness could be demonstrated mainly due to negative results in the older group (-52%). We believe that the effect estimate and its corresponding large confidence intervals in this older subgroup could at least partly be attributed to a lack of sufficient statistical power since the incidence of outcomes in unvaccinated older children was much lower than expected. Residual immunity resulting from exposure to similar influenza strains in previous seasons might also have led to a decreased contrast between unvaccinated and vaccinated children.

As no statistically significant modification of effectiveness across the two seasons was found and the circulating viruses and the vaccine composition differed substantially in both seasons, we pooled the data to enhance statistical power.[30] In vaccinated infants and preschoolers the occurrence of acute respiratory disease was halved (p=0.01), but among the older children no effectiveness was found (p=0.85). Despite the fact that the same children were counted twice in these pooled analysis and observations were therefore statistically dependent, results of mixed effect regression modeling were essentially the same.

Another explanation for finding no effect in the older children and a potential underestimation of the vaccine effectiveness in the younger group could have resulted from incomparability of prognosis among comparison groups. In general, vaccinated children had most probably more severe asthma than unvaccinated children and risk of medically attended respiratory disease resulting from infections is therefore higher in vaccinated children. We have tried to adjust for this so-called 'confounding by indication' by controlling for the various available prognostic indicators in the study design and data analysis.[31] Statistical adjustment led to a substantial increase in the point estimate of the vaccine's protectiveness in the older group. However, confounding by unmeasured factors might also have been responsible for detecting no statistically significant protectiveness.

Studying clinical instead of serological outcomes can lead to non-differential misclassification of outcome values and consequently to an underestimation of the vaccine's effectiveness. This effect has been demonstrated in a recent study by Heikkinen et al. who reported a 83% reduction of influenza-associated acute otitis media by the vaccine, the reduction of acute otitis media overall being 36%.[10,32] Obviously, the difference depends upon the influenza-attributable fraction of outcomes. We restricted our outcome measurements to the influenza seasons where a large proportion of all exacerbations are caused by influenza viruses,[2] and less by other pathogens such as respiratory syncytial- , parainfluenza- , adeno- or rhinoviruses. An advantage of studying clinical instead of serological outcomes is that these data are more relevant from a patient's and physician's point-of-view.

Our study is unique in that it addressed the clinical effectiveness of influenza vaccination on the reduction of acute respiratory disease in asthmatic children. In a prior study by Sugaya et al. the vaccine provided a 49% reduction of influenza-related febrile illnesses in asthmatic children aged 2-14 years,[15] a figure similar to our findings. They found, however, the vaccine to be more effective in children older than seven years of age, but effect modification by age was not statistically confirmed. In 1974 Bell et al. observed a 66% reduction in hospitalization days due to influenza-like-illness and to influenza-like-illness and asthma, but not due to asthma alone.[33] Although both studies, like ours, included asthmatic children, there are some major differences. Neither study measured the effect of vaccination on acute respiratory disease, nor were they primary care-based, multi-season or did they adjust for potential confounders. So far, only protection against acute otitis media has been suggested in healthy children in three prospective, single-season trials, the effectiveness ranging from 30 to 40%.[8-10]

In conclusion, the conventional influenza vaccine appears to offer protection against relevant morbidity in asthmatic infants and preschoolers in return for a safe and relatively cheap intervention. Expansion of the indication range to include children with 'probable asthma' and 'recurring airway diseases' under 6 years of age needs to be seriously considered. Larger studies are needed to establish whether older asthmatic children benefit from the vaccine as well.

Acknowledgment

Physicians of the Utrecht University General Practices Network: Andriesse JA, Asbreuk HAM, Blankestijn JG, Blommestein JG, Bolderink JF, van den Broek MW, Daggelders GJA, de Groot MM, Hendrickx EFHM, Hirsch R, de Jong HHG, Juffermans JMA, Nicolai N, Pieters HM, Rijkens CD, Rutten FH, van der Snoek BE, Stalman WAB, Stoutenbeek IJ, Truijens L, de Wit NJ, van Zijl WLG. Statistical help by Dr J. Faber is gratefully acknowledged.

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CHAPTER 6

Is immunizing all patients with chronic lung disease in the community against influenza cost-effective?

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Is immunizing all patients with chronic lung disease in the community against influenza cost-effective? Evidence from a general practice based clinical prospective cohort study in Utrecht, the Netherlands

Study objective There is little information on the potential benefit of immunizing all chronic lung patients in the community against influenza. The clinical effectiveness and economic benefit was established of the influenza vaccination program in a general practice-based cohort of adult patients with chronic lung disease followed up during the 1995/96 influenza A epidemic.
Design A prospective cohort study from October 1995 to March 1996.
Setting The study was undertaken in the Utrecht General Practices Network with six large group practices, covering a total population of approximately 50,000 patients in The Netherlands.
Patients Computerized medical records of 1696 patients with chronic lung disease aged over 18 years with an indication for vaccination according to the Dutch GP guidelines were reviewed.
Main results The overall attack rate of any complication, including all cause death, low respiratory tract infection and acute cardiac disease was 15%. Exacerbations of lung disease were most frequent (13%). Death, pneumonia, and acute cardiac disease were mainly limited to patients ≥65 years. No effectiveness of the immunization program could be established in patients 18-64 years (N=1,066), after controlling for baseline prognosis in multivariable logistic regression analysis. In vaccinees ≥65 years (N= 630), the occurrence of any complication was reduced by 50% (95% CI 17-70%). The economic benefit was estimated at £50 per elderly vaccinee.
Conclusions Our study suggests that in the Netherlands immunization of elderly patients with chronic lung disease against influenza is effective and cost-saving, hence these patients should be given high priority. More, preferably experimental, studies are needed to establish whether adult lung patients under 65 years in the community will also benefit from vaccination.

Key words: influenza vaccination, asthma, chronic obstructive pulmonary disease, general practice

Published as: Hak E, Essen GA van, Buskens E, Stalman WAB, Melker RA de. Is immunising all patients with chronic lung disease in the community against influenza cost-effective? Evidence from a general practice based clinical prospective cohort study in Utrecht, the Netherlands. *J Epidemiol Community Health* 1998;**52**:120-125

Although annual influenza vaccination has been recommended to all patients with chronic pulmonary disease,[1] immunization rates remain low, particularly in patients under 65.[2-4] These low rates may only be partly the result of concerns about side effects, because many studies have shown no serious

adverse events.[5-8] Scepticism about the impact of influenza in non-institutionalized patients with chronic lung disease is more likely to play an important part. Currently, little information is available on influenza-related mortality and morbidity in this group.[9] Several studies have reported on the effectiveness of influenza vaccination, but most were confined to elderly subjects with or without chronic medical conditions.[10-16] Only a few studies included younger adults, and none considered the effectiveness in patients with chronic lung disease alone.[17-19] This apparent lack of evidence of the potential health and economic benefit resulting from immunizing all patients with chronic lung disease in the community against influenza may explain the poor immunization rates.[9,20]

We aimed to assess the clinical effectiveness of an influenza vaccination program in preventing complications in adult patients with chronic pulmonary disease. We therefore prospectively followed up a general practice-based cohort of patients with lung disease from the moment of vaccination until the end of the influenza A epidemic of 1995/96. Because an age-based immunization policy was recently introduced in The Netherlands, after many other countries,[21] we considered its effectiveness in patients aged under and those aged over 65 years. Finally, we estimated direct costs of medical care associated with the influenza epidemic and immunization program.

Methods

Setting and Study Subjects

The Utrecht University General Practices Network consists of six computerized group practices employing 23 general practitioners (GPs), and covering about 50,000 patients living in the central part of the Netherlands. Since 1989, clinical diagnoses and drug prescriptions have been registered in the medical records using ICPC codes,[22] according to the ICHPPC-2 criteria[23], and ATC codes,[24] respectively. Anonymous data were stored in a central database. The initial step in the enrolment procedure consisted of a computerized search of all potential patients with chronic lung disease in the period October 1993 to October 1995 using a software selection module.[25] The search was based on the following diagnoses: COPD (chronic bronchitis/brochiectasis and emphysema), asthma, malignant and benign neoplasm of the bronchus/lung, tuberculosis, pleurisy, congenital anomalies, and other diseases of the respiratory system. In addition, patients with drug prescriptions from the ATC-subcategory R03 (adrenergics/other anti-

asthmatics) or with a 'lung tag' indicating chronic lung disease only were selected. Participating GPs subsequently classified each initially selected patient as indicated for vaccination or not according to the guidelines of the Dutch College of General Practitioners.[26] All selected high-risk study subjects were invited for vaccination in writing. Patients under 18 years with asthma were not part of our study domain. Both risk of influenza related complications and vaccine effectiveness are different from that of adult lung patients.[9,27]

Influenza vaccination

Mass vaccination of patients who complied with the personal reminder took place in weeks 43 and 44 of 1995. The trivalent sub-unit vaccine was based on H3N2 (A/Johannesburg/33/94-like), H1N1 (A/Singapore/6/86-like), and Influenza B (B/Beijing/184/93-like) strains.[28] All vaccinees were registered.

The 1995/96 Influenza A epidemic

The influenza epidemic started in week 46 (1995) and ended in week 10 (1996).[28] The first and most important peak of influenza activity was observed in December/January and was associated with isolates of influenza A(H3N2), whereas the second peak in February was small and mainly associated with influenza A(H1N1) isolates. The vaccine composition largely matched viral strains isolated from clinical samples collected by the Dutch Sentinel Practice network.[28]

Data collection

Baseline information extracted from the medical records included age, sex, type of health insurance and the number of GP visits during the 12 months prior to vaccination. Medical history data included diagnoses of lung disease (see Setting and Study Subjects) and the following diagnoses of high-risk cardiac co-morbidity:[26] angina pectoris, myocardial infarction, other chronic ischemic heart disease, heart failure, atrial fibrillation/flutter, paroxysmal tachycardia, ectopic beats, pulmonary heart disease, heart valve disease, other heart disease, and pulmonary embolism. Study outcomes were all cause death, exacerbation of pre-existent lung disease, pneumonia, congestive heart failure, acute myocardial infarction, and angina pectoris in week 46 (1995) to week 12 (1996).[10-14,29,30] Acute low respiratory tract illness (LRTI), including pneumonia and exacerbations, was defined as the presence of one or more of the following signs/symptoms presented to the GP: (1) productive cough, (2) wheezy breathing or (3) increased dyspnoe in rest which led to the prescription of antibiotics, beta-2 agonists or corticosteroids. Additional information included hospitalization, length of hospital stay, and use of intensive care facilities. All medical data were checked in the medical records by a physician in April 1996.

Statistical Analysis

We dichotomized age into 18-64 or ≥65 years (retirement age)[1] and underlying lung disease into COPD or asthma.[9] We combined the outcomes all-cause death, acute LRTI, and cardiac disease (CD) to form the primary outcome measure. The two subsidiary outcome measures were any acute LRTI or CD. Univariate analyses were performed to compare vaccinees and non-vaccinees in baseline characteristics using chi-square tests for categorical variables and Student's T-test for continuous variables. Multivariable logistic regression modeling (with EGRET) was used to obtain adjusted estimates and their 95% confidence intervals of vaccine effectiveness.[10,14,31] In the first stage of constructing the model we defined the dependent variable as presence or absence of the primary outcome and the exposure term as vaccination status. We allowed for the potentially confounding variables age, sex, health insurance, lung disease defined as asthma or COPD, presence or absence of cardiac co-morbidity and number of GP visits in the previous 12 months and simultaneously added first-order interaction terms of these variables with vaccination status and age. At this stage it became evident that the interaction term age by vaccination status contributed statistically significant to the model, whereas other interaction terms did not. We proceded by contructing two separate models for both age categories separately. In the final models we only included those variables that substantially altered the estimate of vaccine effectiveness. Regression diagnostics, including distributional and residual plots, and assessment of outliers were used to assess the robustness of the models. Effectiveness was estimated using the formula: (1-OR)*100%.[11] We calculated Mantel-Haenszel weighted relative risks (with EPI-Info) to verify estimates using odds ratios with frequent outcomes.

Economical Analysis

We estimated direct costs of vaccination and combined average costs of hospital stay and use of intensive care facilities from a societal perspective. Net savings were estimated as follows: net savings= immunization costs (including unit costs of vaccines and supplies, promotion, delivery, vaccination and overhead) - costs of medical care averted. The number of outcomes averted was calculated as follows: (N vaccinees) * (attack rate of outcomes among non-vaccinees) * (effectiveness).[11] Immunization costs were estimated at £12.50 per person, including supplies, promotion, delivery, vaccination and overhead. The estimation was based on the total expenses of vaccination which could be claimed by GPs in 1995. Expenses were based on unit costs of vaccin (£4.60) and delivery (£3.60), and £12.90 for patients with private insurance which equals £4.30 on average for all patients. Costs of expenses (or charges) were comparable with direct costs to society. Costs of hospital stay (£168/day) and

intensive care facilities (£821/day) were based on national data.[32] To assess the effects of various estimates on the outcome of the economic analysis, an optimal and worst case scenario were established. We simultaneously varied estimates of effectiveness, proportion of patients needing medical care and median length of hospital stay over a plausible range of plus or minus 20 percent.

Table 1. Baseline characteristics of study subjects (N=1,696). Numbers and percentages (%) are given

Characteristic	Non-vaccinees N=453		Vaccinees N=1,243		P-value
Age category (yrs)					
18-64	361	(80)	705	(57)	<0.001
≥65	92	(20)	538	(43)	
Sex					
Male	268	(59)	621	(50)	<0.001
Female	185	(41)	622	(50)	
Health Insurance					
Private	191	(42)	406	(33)	<0.001
Sick fund*	262	(58)	837	(67)	
Lung disease					
Asthma†	282	(62)	595	(48)	<0.001
COPD‡	171	(38)	648	(52)	
Cardiac co-morbidity¶					
no	425	(94)	1,074	(86)	<0.001
yes	28	(6)	169	(14)	
Number of GP visits in previous 12 months					
low (<3)	383	(85)	923	(74)	<0.001
high (≥3)	70	(15)	320	(26)	

* Compulsory for patients with income lower than £21.500

† In this category patients with pleurisy, other unspecified neoplasm lung, congenital anomalies and other diseases of respiratory tract only are included (N=23)

‡ Chronic Obstructive Pulmonary Disease (in this category patients with neoplasm of lar/trac/bron/lung only are included, N=20)

¶ ICPC codes K74-80, K82-84, K93 (see also Data Collection)

Results

The overall influenza vaccination rate in the 1696 study subjects was 73%. Age-specific immunization rates were 66% (18-64 years) and 85% (≥65 years). At baseline, vaccinees were older (57 versus 47 years, t-value 10.5, p<0.001), more often female, and insured through the Sick Fund than non-vaccinees. Also, COPD, cardiac co-morbidity, and a high GP visiting rate were more common among vaccinees (table 1).

Overall, the attack rate of any complication was 15%, mainly due to LRTI (14%). Exacerbations of underlying lung disease were most frequently observed (12.7%). The occurrence of death (0.5%), CD (1.3%), and pneumonia (1.3%) was less frequent. The recorded primary cause of death was cardiac heart failure (3), pneumonia (2), pneumothorax, cachexis, and ileus (N=8).

In patients aged 18-64 years, the attack rate of any complication in vaccinees was slightly higher than in non-vaccinees (table 2). Acute CD and pneumonia

Table 2. Outcome events (in %) by age-category and vaccination status

	18-64 yrs*		≥65 yrs†		All ages	
Outcome event	**Vac+**	**Vac-**	**Vac+**	**Vac-**	**Vac+**	**Vac-**
LRTI/CD/death‡	12.0	9.7	20.8‡	31.5	15.8	14.1
Low Respiratory Tract Illness (LRTI)						
Exacerbation	10.8	8.6	15.8	22.8	13.0	11.5
Pneumonia	1.1	0.8	1.9	3.3	1.3	1.3
Total LRTI	11.9	9.4	17.7	26.1	14.3	12.8
Cardiac disease (CD)						
Cong. Heart Failure	0.0	0.3	2.0	3.3	0.9	0.9
Angina pectoris	0.0	0.0	0.6	1.1	0.2	0.2
Myocardial infarction	0.1	0.0	0.2	1.1	0.2	0.2
Total CD	0.1	0.3	2.8	5.4	1.3	1.3

* Based on N=1,066
† Based on N=630
‡ Including the deceased (N=8)

were rarely observed, and no deaths occurred. In contrast, the occurrence of any complication in the elderly (≥65 years) was substantially higher, although less common in vaccinees than in non-vaccinees (21 versus 32%).

The results of the multivariable analyses are shown in table 3. In patients aged 18-64 years, no effectiveness of the immunization program in reducing the occurrence of any complication could be established, after adjustment for the prognostic confounding variables underlying lung disease, cardiac co-morbidity, and number of GP visits (adjusted OR 0.95, 95% CI 0.62-1.48, table 3). The inclusion of the other baseline variables age, sex, and health insurance did not confound the association between outcomes and vaccination status. Vaccination in the elderly (≥65 years) was associated with a substantial reduction of the occurrence of any complication (50%), any acute LRTI (46%), or CD (57%, not statistically significant) after adjustments. In patients with cardiac co-morbidity (N=197), the effectiveness in preventing acute CD amounted even to 80% (95% CI 32 to 98%, data not shown).

In all, the hospitalization rate was 1.8%. In 90% of hospitalized patients, one or more of the following risk factors was present: age over 65 years, COPD, cardiac co-morbidity, or a high GP visiting rate. As vaccine effectiveness could only be demonstrated in patients ≥65 years, we limited economic analyses to these subjects (table 4). The hospitalization rate in elderly patients (including the deceased) with LRTI was 9.2% and 45% for elderly with CD. Median hospital stay due to LRTI was 10 days (range 5-20 days) with 1.7% in intensive care, while for CD it was 14 days (range 7-60 days) with 15% in intensive care. In the scenario analyses, we varied effectiveness in preventing LRTI from 26 to 66% and CD from 37 to 77%. Hospitalization rates due to LRTI were varied from 7.4 to 11% and CD from 36 to 54%, while median stay in hospital was varied from 8 to 12 days and from 12 to 16 days, respectively. After subtracting the mean vaccination costs, we estimated the net savings to be £50 (range from £16 to £101) per elderly vaccinee.

Discussion

The findings in this study suggest that influenza vaccination is effective and cost-saving in elderly lung patients, but not in those aged under 65 years. However, some issues need to be considered. Confounding by indication is one of the major threats when studying intervention effects using an observational design. As shown in our study, vaccinees were at higher risk of developing

Table 3. Attack rates, crude and adjusted odds ratio's (OR) and estimated effectiveness (adjusted %) by age-category (N=1,696)

Outcome event	Vaccine status	Attack rate (%)	Crude OR (95% CI)‡	Adjusted OR* (95% CI)	Adj. Effectiveness* (95% CI)
18-64 years (N=1,066)					
LRTI‡/CD¶/death	Vac^+	12.0	1.28 (0.84-1.94)	0.95 (0.62-1.48)	5 (-48, 38)
	Vac^-	9.7			
LRTI	Vac^+	11.9	1.30 (0.85-1.98)	0.97 (0.63-1.52)	3 (-52, 37)
	Vac^-	9.4			
CD	Vac^+	0.1	NA	NA	NA
	Vac^-	0.3			
≥65 years (N=630)					
LRTI‡/CD¶/death	Vac^+	20.8	0.57 (0.35-0.93)	0.50 (0.30-0.83)**	50 (17, 70)
	Vac^-	31.5			
LRTI	Vac+	17.7	0.61 (0.36-1.01)	0.54 (0.32-0.93)$	46 (7,68)
	Vac^-	26.1			
CD	Vac^+	2.8	0.50 (0.18-1.41)	0.43 (0.15-1.24)	57 (-24, 85)
	Vac^-	5.4			

NA Not available. Numbers too small to construct a valid model.

* Regression equation: outcome= ß0 + ß1*(vaccine status) + ß2*(N previous consultations) + ß3*(underlying lung disease) + ß4*(cardiac co-morbidity).

† 95% Confidence Intervals

‡ Low Respiratory Tract Illness, including exacerbations and pneumonia

¶ Cardiac Disease, including acute congestive heart failure, myocardial infarction and angina pectoris

** Adjusted Mantel-Haenszel weighted Relative Risk 0.62 (95% CI 0.45-0.86); variable GP visits dichotomised (<3, ≥3) for stratification

$ Adjusted Mantel-Haenszel weighted Relative Risk 0.63 (95% CI 0.43-0.91)

complications than non-vaccinees, which could have led to an underestimation of the vaccine effectiveness. This confounding may therefore have obscured a potential benefit in the younger age group. Nevertheless, the immunization rate of 66% was high compared with most other vaccination studies,[10-14] which

Table 4. Estimated direct costs (savings) associated with influenza vaccination per 100 vaccinated patients with chronic pulmonary disease (≥65 years) in the Netherlands

Outcome Variable	Estimated costs (in £)
Vaccination (£12,5 per vaccination)	1,250
Medical care avoided for Respiratory Disease*	
Hospital Stay	1,848
Intensive Care	328
Medical care avoided for Cardiac Disease†	
Hospital Stay	3,259
Intensive Care	821
Net total savings	5,007

* Based on 11 days hospital stay (100*0.261*0.46*0.092*10) and 0.4 days intensive care (100*0.261*0.46*0.015*2) for LRTI per 100 vaccinees avoided.

† Based on 19.4 days hospital stay (100*0.054*0.57*0.45*14) and 1 day intensive care (100*0.054*0.57*0.15*2) for CD per 100 vaccinees avoided

probably reduces serious differences in baseline prognosis. Also, the study population was homogeneous with regard to indication criteria and the prevalence of lung disease (36/1,000) was comparable with Dutch general practice morbidity registration data (30-40/1,000).[26,33] Furthermore, we adjusted for some important prognostic confounding variables. The variable underlying lung disease was given by subdividing patients into asthmatic patients and COPD patients in accordance with other studies.[9,34] Misclassification of lung disease was most probably very limited, since participating GPs were extensively trained in classifying lung patients according to ICHPPC-2 criteria. Health-seeking behavior and seriousness of disease were also controlled for by the number of previous GP visits.[14] Nevertheless, we could only adjust for known differences in vaccinees and non-vaccinees. Complete comparability of vaccinees and non-vaccinees with regard to the prognosis of developing influenza-related complications can only be guaranteed in a randomized placebo-controlled trial.

We could not obtain valid information on previous vaccinations. Some reports suggest a reduced effectiveness if patients are vaccinated for the first time.[16,17]

As our GPs have been immunizing lung patients against influenza since the early nineties, it is probable that most vaccinees had been vaccinated more often.

Another possible limitation, like in all other large effectiveness studies,[10-15,17,18] includes the absence of laboratory confirmation of influenza. A sensitive and non-specific definition of clinical outcome may lead to an underestimation of the effectiveness.[14] Although it has not been reported yet, specificity of outcome definitions may be higher in the elderly when compared with the younger age group. This might have contributed to the established differences in effectiveness. Our finding of no effectiveness in younger adults is in agreement with an earlier report by Wiselka and colleagues[3] who could not establish vaccine effectiveness in preventing exacerbations in asthmatics aged 6 to 56 years during the 1989/90 epidemic. Most exacerbations in their study subjects were indeed thought to be caused by viruses other than influenza A. Beasley et al.[27] concluded that only in one-third of severe exacerbations in asthmatics aged 15-56 years could a viral agent be identified. The potential impact of an immunization program on the overall reduction of complications may be at stake when influenza is not the causal agent. Two other cost-benefit studies indicated no financial benefit from immunizing patients under 65 with various medical conditions.[19,35] The authors attributed this to low death and hospitalization rates in the younger age group during an influenza epidemic. We observed no deaths in patients under 65 and hospitalization rates were 3.2 times lower in this group.

The inclusion of acute lung and heart disease as it presents to the GP in the primary outcome measure may be considered a major advantage of this study. The burden-of-illness could mainly be attributed to exacerbations of pre-existing lung disease (13%), whereas a minority of patients (2%) was hospitalized. Studies in which hospitalization and death are the primary endpoints may suffer from more confounding bias, because hospitalization is mainly limited to patients with severe medical conditions as shown in our study.

The fact that all deceased persons were vaccinated reflects a high immunization rate in the elderly subjects (85%). We were not able to confirm influenza as the primary cause of death, hence inferences about vaccination status and mortality are difficult.[36] Our age-specific mortality rate of 1.3% in the elderly was substantially lower than reported by Fleming et al.[14] (3.0% in high-risk elderly) and comparable to rates reported by Nichol et al.[10] who included mostly healthy non-institutionalized elderly. Immunization rates in these studies were lower than in our study (10% and 58%, respectively).

The estimated vaccine effectiveness of 50% in the elderly is in accordance with a recently published large meta-analysis,[13] but net savings appeared to be higher than reported earlier.[10-12] Since indirect costs due to work loss are less important in the elderly, we only calculated direct costs.[10] Furthermore, we decided not to add costs due to consultations for side effects, because only few such consultations occurred in the present study. Possible savings from the reduced number of GP consultations and drug use were even not taken into account. Accordingly, our estimates of net savings may be considered conservative.

Recently, Tirimanna and colleagues[34] showed that more than half the patients with asthma or COPD were not even known to the GP. Although screening on lung function was not part of the present study, it is likely that elderly patients with unknown lung disease could also benefit from vaccination. An age-based vaccination policy may increase the likelihood of reaching all elderly patients with known and unknown high-risk medical conditions in the community.[21]

Our study suggests that in The Netherlands the immunization of elderly chronic lung patients against influenza is effective and cost-saving. A population-based strategy should be developed so that these patients can be identified and immunized efficiently.[25] More studies are needed to establish whether patients with asthma or COPD of working-age should be given priority as well.

Acknowledgment

We thank D.E. Grobbee, professor of Clinical Epidemiology and N. Masurel, professor emeritus of Virology, for useful comments on the manuscript. We are also grateful to mr. A. Lodder for assistance on the statistical part of the study.
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HAM Asbreuk, JG Blankestijn, JG Blommestein, JF Bolderink, GJA Daggelders, MEL van Dillen, WH Eizenga, MM Groot, EFHM Hendrikckx, R Hirsch, HHG de Jong, JMA Juffermans, ME Numans, HM Pieters, CD Rijkens, FH Rutten, BE van der Snoek BE, Y Stoutenbeek, L Truijens, W Stalman, MW Vorst-van den Broek, NJ de Wit, WLG van Zijl.

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CHAPTER 7

Lack of effectiveness of conventional influenza vaccination among patients with asthma or COPD of working-age

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Lack of effectiveness of conventional influenza vaccination among patients with asthma or COPD of working-age

Background Little is known about the clinical benefits of influenza vaccination among patients of working-age with asthma or COPD. We determined the effectiveness of the vaccine in reducing morbidity from influenza among these patients during the 1998—1999 and 1999—2000 influenza epidemics.

Methods We conducted a prospective nested case-control study in 41 (season one) and 52 (season two) primary care centers. Eligibility criteria included age 18—64 years with asthma or COPD (4241 and 5966 patients). Patients developing fatal or non-fatal exacerbations of lung disease, pneumonia, heart failure, or myocardial infarction during either epidemic were considered cases. For each case, four age- and sex-matched controls were randomly sampled and patient records were reviewed. We obtained nose-throat swabs from a sample of cases and controls for virological assessment. We used conditional logistic regression and propensity scores to assess vaccine effectiveness after adjustment for confounding factors.

Results Severe morbidity, mainly respiratory, occurred in 13/1000 in season one and 34/1000 in season two. Eighty-seven percent (47/54) of cases had been vaccinated in season one, and 85 percent (171/202) in season two; figures for controls were 74 percent (155/210) in season one and 75 percent (575/766) in season two. After adjustments, vaccination was not associated with reductions in complications (season one: odds ratio 0.94; 95 percent confidence interval, 0.26 to 3.48, season two: odds ratio 1.09; 95 percent confidence interval, 0.60 to 1.97, pooled odds ratio: 1.07; 95 percent confidence interval, 0.63 to 1.80). Ten of 22 cases (46 percent) in season one and 11/20 (55 percent) in season two had influenza infection compared with only one positive control.

Conclusions Influenza-associated respiratory morbidity in epidemics is high among 18 to 64-year-old patients with asthma or COPD. Conventional influenza vaccination does not appear to prevent this morbidity.

Key words: influenza, lung diseases, vaccines, immunization, case-control studies, middle age

Submitted as: Hak E, Hoes AW, Grobbee DE, Lammers JWJ, Van Essen GA,Van Loon AM, Verheij TJM. Lack of effectiveness of conventional influenza vaccination among patients with asthma or COPD of working-age.

The risk of influenza-related morbidity and mortality during influenza epidemics is high[1-4] and vaccination against influenza yields substantial clinical benefits in elderly patients with chronic pulmonary disease.[5,6] Relatively little information, however, is available for patients of working-age with chronic pulmonary disease. Some studies showed that these patients may account for many hospital admissions for respiratory illness during epidemics, but risk

estimates are largely unknown.[7-9] On the other hand, the sparse data available on acute respiratory illness in asthmatics suggests a relatively minor role for influenza.[10-11] The view available small-scale studies on clinical benefits of influenza vaccination among patients with chronic pulmonary disease of working-age failed to demonstrate any effectiveness from annual vaccination[6,13,14] whereas the vaccine can lead to potential adverse effects.[12]

We determined the occurrence of respiratory and cardiac morbidity associated with influenza and the clinical effectiveness of vaccination in reducing these complications in patients with asthma or COPD aged 18—64 years using a prospective nested case-control design. Our observations covered the 1998—1999 outbreak (principally type B), and the 1999—2000 epidemic (mainly type A (H3N2)).[15,16]

Methods

Source population

Study patients were chosen from among primary care patients between 18 and 64 years old with asthma or COPD targeted according to immunization guidelines for annual influenza vaccination.[17,18] Seventy-eight general practitioners in 41 computerized primary care centers across the Netherlands participated in the study in the 1998—1999 influenza epidemic and 93 general practitioners in 52 centers in the 1999—2000 epidemic. These general practitioners routinely integrate all patient information in their computerized records using ELIAS (SMS Cendata, Nieuwegein).[19]

Patients eligible for inclusion into our study were selected as of October 1999 and October 2000 by means of a dedicated software module. Details on the module's stepwise selection procedures have been described elsewhere.[20] Briefly, patients were identified by their age, and presence of chronic pulmonary disease as indicated by International Classification of Primary Care (ICPC) diagnostic codes (R91, R95, R96), Anatomical Therapeutic Classification (ATC) medical drug codes (Class R03), and a tag in their computerized records indicating chronic pulmonary disease. Next, the general practitioners verified whether the diagnoses of asthma or COPD in the pre-selected patients had been made in accordance with the guidelines of the Dutch College of General Practitioners.[21] In October 1999 4241 and in October 2000 5966 eligible patients were enrolled. The Medical Ethical Board of the University Medical Center Utrecht approved the conduct of the study.

Identification of cases during the epidemics

Subjects qualified as a case if they had a primary diagnosis of an episode of fatal or non-fatal severe exacerbation of underlying lung disease, pneumonia, congestive heart failure or myocardial infarction during either epidemic (see Appendix). Case criteria were verified using a computerized questionnaire, integrated in the medical records of study patients that could be activated by their general practitioner during consultation.

Annual influenza surveillance was carried out by the National Influenza Center in collaboration with the Sentinel Practice Network.[15,16] The epidemic periods were defined as between week 50 of 1998 and week 12 of 1999 (season one), and between week 50 of 1999 and week 10 of 2000 (season two). During the first and largest wave of the 1998—1999 bi-phasic influenza outbreak, the influenza B-Harbin-type virus predominated, followed by a smaller wave of A(H3N2)Sydney type. Clinical influenza activity during the 1999—2000 season was predominantly associated with influenza A(H3N2)Sydney-type.

In season one six of 60 cases were deemed ineligible because their diagnosis of chronic pulmonary disease was unclear and five of 207 in season two, and these patients and their controls were excluded from further consideration. In season one and two, 47 and 174 patients with severe exacerbation of asthma or chronic obstructive lung disease, 5 and 26 patients with pneumonia, zero and one patient with congestive heart failure, and two and one who died were eligible cases. No myocardial infarctions were recorded. In season one and two, respectively, 8 and 16 cases were hospitalized.

Identification of controls

Each time a case occurred, we randomly selected four control patients from the remainder of that season's cohort, matched for age (in the same 5-years age-category) and sex. Of the 1024 controls selected from the database, 50 were excluded because either no data were available for them or baseline diagnosis was unclear, or because they had died or been lost to follow up before the relevant epidemics.

Assessment and confirmation of exposure to influenza vaccine

In the Netherlands, most patients receive the influenza vaccine through a vaccination program in primary care.[17] The composition of the trivalent sub-unit influenza vaccine complied with WHO recommendations and matched well with circulating influenza A and B strains in both seasons.[15,16] A person was assumed to have been vaccinated if their general practitioner retrospectively confirmed the receipt of influenza vaccination by review of

Appendix. Case definition

Respiratory illness	Cardiac illness	Death
Severe exacerbation of asthma/ COPD	*Congestive heart failure*	
At least 1 of 4 criteria: 1. Confirmation by a pulmonologist; 2. FEV1 <60% predicted; 3. PEF <70% of personal best; 4. ≥3 signs and symptoms or ≥2 and the use of oral corticosteroids: - insufficient recovery; - expiratory wheezing; - cough; - increased dyspnoea; - insomnia; - sputum production; - exhaustion.	At least 1 of 2 criteria: 1. Confirmation by a cardiologist; 2. At least 3 of the following signs and symptoms and prescription of furosemide: - edema; - increased central venous pressure or hepatomegaly; - signs of pulmonary congestion or hydropneumothorax; - enlarged heart; - dyspnoea.	At least one criterion: 1. Primary cause of death is influenza, exacerbation of asthma/ COPD, pneumonia, congestive heart failure, myocardial infarction; 2. Sudden cardiac death (<1 hour after first symptoms and cardiac cause not excludable).

Respiratory illness	Cardiac illness
Pneumonia (with or without influenza)	*Myocardial infarction*
Presence of at least one criterion: 1. Confirmation by X-ray; 2. Three or more of the following signs/ symptoms: - decreased intensity for breath sounds; - dullness on chest percussion; - inspiratory crackles; - bronchophony; - fever (≥38 °C); - local chest pain on deep inhalation.	At least 1 of 2 criteria: 1. Confirmation by a cardiologist; 2. At least 2 of the following signs and symptoms < 8 weeks: - angina (>15 minutes) indicating myocardial ischemia; - abnormal ST-T changes or Q-elevations on ECG; - increased heart enzymes.

medical records. Confirmed (non-) exposure to influenza vaccination within the two months before either epidemic was in high agreement with the absence/presence of the ICPC-code for vaccination R44.1 (kappa was 93 percent).

Measurements of covariates

Base-line demographic information, including age, sex and health insurance cover (private or National Health Service) was collected using the software module.[20] Further detailed information was obtained on potential risk factors by review of medical records, particularly the presence of concomitant high-risk disease and previous hospital admissions in the 12 months preceding the epidemic. Also, influenza infection and influenza vaccination status in the previous season and chronic use of medications was registered, and the numbers of consultations in the preceding year were counted as an indicator of disease severity and medical consumption.

Virology

Six primary care centers with 23 trained general practitioners from the Utrecht academic network[6] were asked to take nose and throat swabs from their cases and a sample of controls for virological assessment. Specimens were put into 4 ml. transport medium. Swabs were vortexed for 10s and centrifuged at 2,000 *g for 15 min. One milliliter of the supernatant was used directly for virus culturing. The other material was stored at –70 °C. Nested reverse transcriptase polymerase chain reaction was carried out blindly to test for the presence of influenza A or B virus, respiratory syncitial virus, picornaviruses (rhinovirus and enterovirus), para-influenza viruses 1, 2 and 3 and coronavirus.[22]

Sample size and data analysis

Before starting the study, we estimated that a seasonal study population of 186 cases and 744 controls would give us a statistical power of more than 80 percent to detect an odds ratio of 0.6 (i.e. reduction of 40 percent),[3-5] assuming a vaccination rate of 75 percent, a case—control ratio of 1:4 and a two-tailed α level of 0.05.

We approached data-analysis in two ways. First, we applied multivariate conditional logistic regression analysis for matched case-control studies to assess the vaccine effectiveness independent of confounding factors. In the modeling procedure, factors that appeared to be strongly associated with both exposure to vaccination and the case status were first added to the naive model including vaccination status only. Additionally, those risk factors that substantially altered the odds ratio of vaccine effectiveness further (>5 percent) were entered in the

model.[23] Since circulating viruses and vaccination components differed in the two seasons, and only a minority of subjects were admitted during both, we pooled the observations and performed similar analyses on case and control person-periods.[24] Moreover, we decided in advance to determine potential modification of vaccine effectiveness by age (18 to 39, 40 to 64 years), sex, disease (asthma or COPD), and care by a pulmonologist, using statistical interaction terms. Adjusted odds ratios, as approximations of relative risks, and their 95 percent confidence intervals were calculated.

Next, we applied the propensity score method, which is a recently introduced powerful method of further removing 'confounding by indication'.[25,26] This technique enables assessment of the association of an intervention, i.e. vaccination, with outcomes in patients with an equal probability of receiving the vaccine. All potential predictors were included in a logistic regression analysis with vaccination as the dependent variable. The analysis was used to estimate the probability of vaccination (propensity score) for each individual patient in the full data-set (256 cases, 976 controls). The fit of the model, including age and sex, health insurance, underlying disease, use of prednisolone and inhaled corticosteroids, specialist care, and cardiac and other co-morbidity was appropriate (Hosmer Lemeshow goodness-of-fit test: p=0.41), and the model's discriminative ability was moderate to good with an area under the receiver-operating curve (AUC) value of 0.71 (95 percent confidence interval, 0.68 to 0.75). In a patient-matching procedure, we searched for a vaccinated person who had the closest propensity score (within a range of 0.00 to 0.01) for each unvaccinated patient. Thus, in this quasi-experiment, two comparison groups with equal probability of vaccination were formed and, in analogy to the analysis of trials, cumulative incidences of complications are compared.

Results

The overall cumulative incidence of complications —mainly respiratory— was 13 per 1000 in the first and 34 per 1000 in the second season (table 1). Influenza morbidity was highest among the older age group (45 to 64 years), females and those with COPD.

Vaccinated subjects were older and had a higher prevalence of COPD, and cardiac and other co-morbidity, and were more often insured through the National Health Service than unvaccinated subjects (table 2). In addition, they had higher GP consultation and hospitalization rates in the 12 months

Table 1. Cumulative incidence (per 1000) of influenza-associated morbidity and mortality by age, sex and pulmonary disease during the two influenza seasons

	1998—1999 influenza B epidemic (N = 4241)				1999—2000 influenza A epidemic (N = 5966)			
Characteristic	**Exacerbation of asthma/COPD†**	**Pneumonia**	**Other⋆**	**All**	**Exacerbation of asthma/COPD†**	**Pneumonia**	**Other⋆**	**All**
Age (years)								
18-44	6	0.0	0.0	6	14	2	0.0	16
45-64	17	3	1	21	46	7	0.4	53
Sex								
male	7	0.5	0.5	8	25	4	0.4	30
female	15	2	0.4	18	32	5	0.0	37
Lung disease								
asthma	10	1	0.0	10	25	3	0.2	29
COPD†	15	2	2	18	39	8	0.0	48
Total	11	1	0.5	13	29	4	0.2	34

⋆ Other denotes death (two in 1998—1999 season, one in season 1999—2000) or congestive heart failure (one case in 1999—2000 season)
† COPD denotes chronic obstructive pulmonary disease

Table 2. Characteristics at base-line and during influenza seasons (estimated from controls) according to vaccination*

Characteristic	Base-line cohort season 1998—99			Influenza season 1998—1999			Influenza season 1999—2000		
	Vaccinated (N = 2687)	Unvaccinated (N = 1414)	P value of difference	Vaccinated (N = 147)	Unvaccinated (N = 63)	P value of difference	Vaccinated (N = 564)	Unvaccinated (N = 202)	P value of difference
Mean age, yr	44.3	37.3	<0.001	51.2	48.2	0.06	51.6	45.4	<0.001
Male (%)	43.8	49.7	0.001	50.3	44.4	0.43	49.5	55.4	0.15
National Health Service (%)	70.6	62.5	<0.001	67.3	62.3	0.33	70.6	57.9	0.001
COPD (%)	31.9	20.4	<0.001	44.2	31.7	0.09	43.3	28.7	<0.001
Cardiac disease (%)				4.8	3.2	0.60	21.0	0.0	<0.001
Other high-risk disease (%)				7.5	4.8	0.47	8.0	2.0	0.003
Previous health care use†									
GP visits ≥4 (%)				10.2	6.3	0.15	10.8	3.0	<0.001
Hospitalization (%)				4.8	0.0	0.079	5.1	2.0	0.058
Pulmonologist care (%)				23.8	6.3	0.003	24.8	6.9	<0.001
Influenza infection (%)				22.4	12.7	0.10	22.0	9.9	<0.001
Influenza vaccination (%)				89.1	22.2	<0.001	88.5	22.8	<0.001
Antibiotics (%)				29.9	20.6	0.17	26.1	14.9	0.001
Inhaled corticosteroids (%)				63.9	57.1	0.35	59.4	42.1	<0.001
Oral corticosteroids (%)				16.3	4.8	0.022	18.3	7.4	<0.001
Bronchodilators (%)				59.2	60.3	0.83	64.2	46.5	<0.001

* ICPC-code R44.1 used as an indicator for vaccination status; no review of patient records was undertaken for the total base-line cohort (N = 4241)

† previous health care use refers to the period of 12 months before October of 1999 or 2000

Table 3. Influenza vaccination and risk of influenza-associated complications

Influenza vaccination	Cases	Controls	Adjusted for:	Adjusted odds ratio (95 percent confidence interval)*
1998—99 influenza epidemic	N = 54	N = 210		
Influenza vaccine prior to 1998—99 epidemic—(%)	87.0	73.8	age and sex (matching factors)	2.33 (1.00—5.40)
			+ influenza vaccination in 1997	1.36 (0.47—3.97)
			+ specialist care	1.25 (0.43—3.64)
			+ prednisolone	0.94 (0.31—2.83)
			+ 8 remaining factors†	0.95 (0.26—3.48)‡
1999—2000 influenza epidemic	N = 202	N = 766		
Influenza vaccine prior to 1999—2000 epidemic—(%)	84.7	74.8	age and sex (matching factors)	1.81 (1.17—2.78)
			+ influenza vaccination in 1998	1.21 (1.11—2.10)
			+ specialist care	1.11 (0.62—1.99)
			+ prednisolone	1.09 (0.60—1.97)
			+ 8 remaining factors†	1.07 (0.59—1.96)§
Pooled analysis	N = 256	N = 976	all factors	1.07 (0.63—1.80)¶
Influenza vaccine prior to either influenza epidemic—(%)	85.2	74.6		

* reference category is no vaccination; analysis performed by use of conditional logistic regression analysis

† disease (asthma/ COPD), health insurance, GP visits, use of antibiotics, inhaled corticosteroids or bronchodilators, cardiac or other morbidity

‡ interaction for age: p=0.21; for pulmonary disease: p=0.73; for sex: p=0.46; for specialist care: p=0.93

§ interaction for age: p=0.44; for pulmonary disease: p=0.83; for sex: p=0.47; for specialist care: p=0.96

¶ interaction for age: p=0.46; for pulmonary disease: p=0.44; for sex: p=0.22; for specialist care: p=0.93

Table 4. Base-line characteristics and outcomes using the propensity score (N=514)

Characteristic	Vaccinated (N = 257)	Unvaccinated (N = 257)	P value of difference
Mean age, yr	45.9	45.7	0.83
Male — no. (%)	141 (54.9)	129 (50.2)	0.29
National Health Service — no. (%)	148 (57.6)	150 (58.3)	0.86
COPD — no. (%)	80 (31.1)	75 (29.2)	0.63
GP visits ≥4 — no. (%)	12 (4.7)	19 (7.4)	
Cardiac co-morbidity — no. (%)	3 (1.2)	2 (0.8)	0.65
Other high-risk disease — no. (%)	8 (3.1)	8 (3.1)	1.0
Previous hospitalization — no. (%)	3 (1.2)	7 (2.7)	0.20
Inhaled corticosteroids — no. (%)	136 (52.9)	125 (48.6)	0.33
Oral corticosteroids — no. (%)	20 (7.8)	26 (10.1)	0.35
Bronchodilators — no. (%)	152 (59.1)	139 (54.1)	0.25
Treatment by pulmonologist — no. (%)	29 (11.3)	29 (11.3)	1.00
Influenza in previous season — no. (%)	32 (12.5)	34 (13.2)	0.79
Outcome*			
Exacerbation— no. (%)	30 (11.7)	31 (12.1)	0.91
Pneumonia— no. (%)	3 (1.2)	1 (0.4)	0.25
All complications— no. (%)	33 (12.8)	32 (12.5)	0.89

* Outcomes of the two influenza seasons combined

Table 5. Viral etiology of complications during the two influenza epidemics

	1998—1999 influenza B epidemic (N = 56)*		1999—2000 influenza A epidemic (N = 44)†	
Viruses — No. (%)	**Cases (N = 22)**	**Controls (N = 34)**	**Cases (N = 20)**	**Controls (N = 24)**
Influenza A virus	8 (36)	0 (0)	11 (55)	1 (4)
Influenza B virus	2 (9)	0 (0)	0 (0)	0 (0)
Influenza A or B virus	10 (46)	0 (0)	11 (55)	1 (4)
Rhino virus	2 (9)	0 (0)	2 (10)	1 (4)
Corona virus	1 (5)	0 (0)	2 (10)	1 (4)
Entero virus	0 (0)	0 (0)	0 (0)	0 (0)
Respiratory syncitial virus	0 (0)	0 (0)	0 (0)	0 (0)
Parainfluenza virus	0 (0)	0 (0)	0 (0)	0 (0)

* 25 cases and 95 controls reported; no samples taken from 3 cases and 61 controls
† 29 cases and 136 controls reported; no samples taken from 9 cases and 112 controls

preceding base-line and had more often been vaccinated against influenza in the previous season.

Eighty-seven percent of cases and 73.8 percent of controls had been vaccinated in season one, and 84.7 percent of cases and 74.8 percent of controls in season two (table 3). After adjustment for matching variables age and sex, and potential confounders, the vaccine was apparently not associated with any reduction in the incidence of complications (season one: adjusted odds ratio 0.94; 95 percent confidence interval, 0.26 to 3.48, season two: odds ratio 1.09; 95 percent confidence interval, 0.60 to 1.97, pooled odds ratio 1.07; 95 percent confidence interval, 0.63 to 1.80). Also, vaccine effectiveness was not significantly modified by age, sex or underlying pulmonary disease, or care by a pulmonologist.

In the propensity score analysis, outcome rates in the 257 vaccinated and 257 unvaccinated subjects matched on the equal probability of being vaccinated were equal (relative risk; 1.03, 95 percent confidence interval, 0.66 to 1.62, see table 4).

Assessment for presence of influenza viruses in a sample of cases and controls (see methods) showed that in season one 10/22 cases (46 percent) and in season two 11/20 cases (55 percent) were positive for either influenza A or B, whereas only one control had influenza infection (see table 5). Other respiratory viruses were relatively infrequently found in the cases.

Discussion

In this study we showed that, although influenza-associated respiratory morbidity is common among patients of working-age with asthma or COPD, there is no evidence that the annual conventional inactivated trivalent sub-unit influenza vaccine reduces the incidence rate of these complications.

Since patients with asthma or COPD are strongly recommended for influenza vaccination, the vaccine effectiveness can not be assessed in a placebo-controlled trial. The case—control approach enables the assessment of the effects of vaccination on severe end points with a relatively low incidence. An advantage of the nested case-control study includes the reduction of bias due to inappropriate selection of controls. Exposure rates in controls were similar in both seasons and comparable with those figures in the base-line cohort. Although the control patients were somewhat older than the total cohort, the distribution of some important characteristics in vaccinated and unvaccinated controls was comparable with that of the base-line cohort. Furthermore, a potential recall bias was minimized through the use of computerized medical records.

Several potential limitations of our study need to be considered. A major issue in non-experimental evaluation of vaccines is often that vaccinated and unvaccinated patients are not prognostically comparable. As expected and shown by the present and previous studies, vaccinees have more risk factors than non-vaccinees.[4-6,24,27] This may have obscured a positive effect of vaccination. However, we minimized this so-called 'confounding by indication'[23] in both the design and data-analysis phases of the study. First, we only admitted into the study cohorts patients with current asthma or COPD. Recent studies have shown that only in a few patients registered as having asthma or COPD were the diagnoses not confirmed by spirometry.[28,29] Second, since age and sex are major confounders, we matched cases and controls for these factors. Third, we had information on many potential confounders and we adjusted for these by conditional logistic regression. Once we had controlled for the matching factors and just three additional risk factors (previous vaccination, specialist care and prednisolone use in the previous year), further adjustment for eight additional risk factors did not alter the estimates of vaccine effectiveness. Finally, we applied the propensity score method as an effective technique to control for 'confounding by indication'.[25,26] Although the statistical power of the latter approach was more limited, risk factors were apparently similarly distributed in the selected vaccinated and unvaccinated subjects and there was no difference in incidences of outcomes. Obviously only

a large randomized controlled trial will guarantee absence of confounding, but it is very unlikely that the observed lack of vaccine effectiveness in our non-experimental study could be explained by residual confounding in our data.

Most studies of the effectiveness of vaccine among the elderly have been restricted to even more severe end points such as death or hospitalization for influenza or pneumonia, assuming that during influenza outbreaks the influenza is frequently a causal component of these outcomes.[30,31] However, from a societal point of view, the influenza-related needs for health care of patients of working-age are mainly limited to relatively less severe complications treated in primary care or at outpatient clinics. Rothbarth and colleagues, for example, estimated that in the Netherlands 11 excess deaths occur among this group of half a million persons during influenza epidemics.[14] In other words, if the vaccine would be able to prevent 50 percent of deaths,[5] over 100,000 patients need to be vaccinated to prevent one death. A major strength of our study is that virological analyses of a sample of our cases and controls showed that influenza infection was frequently associated with these complications, and we found much higher prevalences than reported in earlier influenza studies in this age group.[10-11] Although a positive relation between respiratory virus infections and exacerbations of asthma has been well established, the etiological role of influenza viruses has long been underestimated. This might mainly be due to the laboratory techniques used to detect these viruses, and in recent years, PCR has become available for rapid diagnosis of influenza infection, considerably increasing diagnostic accuracy compared with conventional virological analysis.[22,32]

This study is one of the largest so far reported and it covered two types of influenza outbreaks. Although we had limited power to detect a clinically important reduction of at least 40 percent in the first season, in the second season and pooled data from the two seasons combined, including 256 case person-periods and 976 control person-periods, provided enough power to estimate an even smaller reduction of 35 percent.

Our finding of a lack of any health benefit from influenza vaccination in respiratory patients of working-age corroborates some earlier observations. Paul et al., for example, observed no reduction in acute respiratory illness in a small subset of vaccinated high-risk patients under 65 years of age during the 1985—1986 influenza epidemic.[33] Stenius and colleagues also found no protective effect of the vaccine in reducing asthma exacerbations in a randomized controlled trial among asthmatics.[34] Wiselka and colleagues conducted a general practitioner-based study among more than 500 adult asthmatics and found that

influenza vaccination was not associated with any substantial reduction in either asthma exacerbations or severity of symptoms.[35]

These observations seem counter-intuitive in the face of the beneficial effects of conventional influenza vaccination in high-risk children and the elderly, and they do not support international recommendations to immunize patients of working-age with asthma or COPD against influenza.[18] It is still unclear why the vaccine is clinically not effective in this patient group. One possible explanation could be that virus-induced allergy and hyper-reactivity as precipitating factors may be a much more significant pathological mechanism in adults than in young children and the elderly.[11,36,37] If this is true, preventive measures other than vaccination against influenza such as self-management programs aiming at reducing number and severity of exacerbations of asthma or COPD may have a larger impact on the influenza-related health burden in this particular group of high-risk patients than does annual influenza vaccination.

Acknowledgements

The participation of the general practitioners in the data collection is gratefully acknowledged. We are indebted to Ir. F. Leffers for the technical assistance. We also thank Dr. M. Nijhuis and Mrs. L. van Elden for the virological analyses. The Netherlands Asthma Foundation financially supported this study (No. 97.51).

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CHAPTER 8

Influence of high risk medical conditions on the effectiveness of influenza vaccination among elderly members of three large managed care organizations

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Influence of high risk medical conditions on the effectiveness of influenza vaccination among elderly members of three large managed care organizations

Background Little is known about the influence of specific high risk medical conditions on the risk for the serious complications of influenza or the effectiveness of influenza vaccination among the elderly. We therefore conducted this serial cohort study to assess the risk for hospitalization or death and the effectiveness of influenza vaccination among subgroups of elderly members of three geographically disparate US managed care organizations including persons with cardiopulmonary disease, diabetes, immune-suppression, other high-risk conditions and healthy elderly.
Methods For the 1996-97 and 1997-98 influenza seasons, the following data were obtained on elderly members of each plan using administrative and clinical computer databases: demographic information, baseline health care use, co-morbid conditions, influenza vaccination status, and outcomes during the influenza seasons (hospitalization for pneumonia and influenza (P&I) and all-cause death). Outcomes in vaccinated and unvaccinated elderly members according to risk and disease specific subgroups were compared after controlling for age, gender, other co-morbidities and prior health care use.
Findings 122,974 and 158,454 elderly persons were included in the two study cohorts. The vaccination rates were 57.7% the first year and 58.1% the second year. Among unvaccinated persons, hospitalizations for pneumonia and influenza or death occurred in 8.2/1,000 healthy persons and 38.4/1,000 high-risk persons in year 1 and 8.2/1000 and 29.3/1000 in year 2. After adjustments, vaccination was associated with a 48% reduction in the combined outcome of hospitalization or death (95% confidence interval (CI) 42% to 52%) in year 1 and 31% (95% CI 26% to 37%) in year 2. Effectiveness estimates were statistically significant and generally consistent across the healthy and high-risk subgroups in both years. The absolute risk reduction, however, was higher among high-risk persons than among healthy elderly persons in each year (18.0 events prevented with vaccination per 1000 high risk persons vs 3.8 events per 1000 healthy persons in year 1 and 8.5 events prevented with vaccination per 1000 high risk persons vs 3.5 events per 1000 healthy persons in year 2). For years 1 and 2, 55 and 118 high risk persons needed to be vaccinated to prevent one hospitalization or death. Among healthy persons, 264 and 290 needed to be vaccinated in order to prevent one outcome.
Interpretation Influenza causes significant morbidity and mortality in all subgroups of elderly persons and individuals in both high risk and healthy subgroups may substantially benefit from vaccination. However, the impact of influenza is highest in those with high-risk medical conditions.

Key words: Influenza, immunization, elderly, administrative database, epidemiology

Submitted as: Hak E, Nordin J, Wei F, Mullooly J, Poblete S, Strikas R, Nichol KL. Influence of high risk medical conditions on the effectiveness of influenza vaccination among elderly members of three large managed care organizations.

Annual influenza epidemics continue to impose an enormous health and economic burden on society, especially among the elderly.[1,2] Immunization against influenza has been demonstrated to be effective in reducing associated

morbidity and mortality[3-6] and cost-saving among seniors.[7] Despite evidence for its cost-effectiveness, however, current immunization rates remain unsatisfactory. In the United States, for example, more than 30% of the elderly fail to receive the vaccine each season.[8] Similarly low vaccine uptake rates have been reported in other countries.[9] Apart from differences in health care, studies have shown that among the main reasons for compliance with vaccination recommendations are the recommendations of health care providers and belief in the impact of influenza and the safety and effectiveness of the vaccine.[10-12]

Underlying conditions, such as cardio-pulmonary disease, are well known risk factors for serious influenza-associated complications.[3-6,13,14] However, the clinical effectiveness of influenza vaccination among persons with specific chronic, high risk medical conditions has not been well described, and this may lead to uncertainties regarding the benefits of vaccination in these groups. On the other hand, information on the rates of serious complications of influenza in healthy elderly are limited and suggest a lower impact than among elderly with high-risk disease.[15,16] Two previous cohort studies were inconclusive with regard to benefits in low risk seniors.[17,18] These findings may help to explain suboptimal vaccination rates in seniors and likely have contributed to widespread international variation in immunization recommendations.[19]

Age-based immunization policies are attractive both from an organizational and health- economical point of view. However, additional information clarifying issues of individual risk for the serious complications of influenza and the benefits of vaccination may help policy makers and program planners design more effective vaccination programs or to prioritize vaccine delivery when vaccine supplies are inadequate.[20,21] In a prospective cohort study using administrative and clinical databases of three health plans in the US, we therefore determined the occurrence of influenza and pneumonia hospitalizations and death from all causes during the 1996-97 and 1997-98 influenza epidemics, and the effectiveness of influenza vaccination in preventing these outcomes in specific high-risk subgroups of elderly plan members. These subgroups included persons with cardiopulmonary disease, diabetes, immune-suppression, other high risk diseases and healthy elderly.

Methods

Setting

This study is part of an ongoing collaborative effort between three large managed care organizations from geographically disparate locations across the US to pool data derived from their linked administrative and clinical databases in order to provide timely assessments of influenza vaccination effectiveness. HealthPartners (HP) is a nonprofit health maintenance organization with about 890,000 members in Minnesota and Wisconsin. It offers coverage for 280,000 members through a staff model health maintenance organization, while the other members are covered through a network health maintenance organization model. Kaiser Permanente Northwest Division (KPNW) provides health care services to nearly 420,000 persons in Portland, Oregon-Vancouver, Washington. Oxford Health Plans (Oxford) provide health benefit plans to 1.8 million members in New York, New Jersey, Pennsylvania and Connecticut. In all, over 3 million members receive medical care from these health plans. For study purposes, the same definitions for diagnoses and outcomes were used.

Study subjects

Eligibility criteria to be included in the two study cohorts were: member of one of the three health plans aged 65 years or older as of October 1, 1996 in the first year and October 1, 1997 for the second year and continuous enrollment for the one-year period prior to October 1 for each study year through the outcome period. The continuous enrollment period was required to ensure complete capture of outcome data as well as enough prognostic information to allow for adjustment of potential incomparability between comparison groups.[22] The health plans cover institutionalized persons as well community dwelling persons. Because capture of vaccination status was thought to be incomplete for institutionalized people, they were excluded from the study. For the 1996/97 and 1997/98 study years, there were 122,974 and 158,454 eligible plan members among the three health plans, combined.

At baseline, eligible subjects were classified into seven non-mutually exclusive groups according to entries of relevant codes in the *International Classification of Diseases, Ninth revision, Clinical Modification* (ICD-9-CM) in outpatient clinic or hospital databases 12 months prior to September 30, 1996 in year 1 and September 30, 1997 in year 2: (1) combination of pulmonary (ICD-9-CM codes 011, 460, 462, 465-66, 480-511, 512.8, 513-17, 518.3, 518.8, 519.9, 714.81) and cardiac disease (ICD-9-CM codes 093, 112.81, 130.3, 391, 393-98, 402, 404, 410-29, 745-6, 747.1-747.49, 759.82, 785.2, 785.3), (2) pulmonary disease, (3) cardiac disease, (4) diabetes and other endocrine disorders (ICD-9-

CM codes 250-1), (5) immune suppression [renal disease (ICD-9-CM codes 274.1, 403, 580-91, 593.71-593.73, 593.9), immune-deficiency or organ transplants (ICD-9-CM codes 042, 079, 279, V08, V42), hematological cancer (ICD-9-CM codes 200-208) or non-hematological cancer (ICD-9-CM codes 140-198, 199.1)], (6) other comorbid conditions [dementia or stroke (ICD-9-CM codes 290-4, 331, 340-1, 348, 438), vasculitis or rheumatologic diseases (ICD-9-CM codes 446, 710, 714 - 714.4, 714.8, 714.89, 714.9), and (7) healthy elderly (having none of the previously listed diagnostic codes in their records). Other baseline data that were obtained included age and gender, number of any hospitalizations or outpatient visits, and whether a person had a hospitalization for influenza or pneumonia in the previous year.

Influenza vaccination and seasons

The health plans offered their members vaccination with the trivalent inactivated influenza virus vaccine current for each season. During the 1996-97 epidemic influenza activity was widespread in most US states, exceeding baseline levels for more than 5 consecutive weeks. Circulating influenza strains predominated by the H3N2 A-type matched well with the components of the vaccine of that year.[23] In 1997-98, the level of influenza activity was similar, but another influenza A virus, the A/H3N2/Sydney-like virus, became the predominant strain in most areas in the US.[24] That year's vaccine containing A/H3N2/Wuhan-like virus was poorly matched to the predominant circulating virus. Influenza seasons were defined as follows on the basis of influenza surveillance data from the Centers for Disease Control: Year 1: HealthPartners: November 22, 1996 through May 24, 1997; Oxford: October 5, 1996 through May 3; Kaiser: November 22, 1996 through March 22. Year 2: HealthPartners: December 7, 1997 through March 28, 1998; Oxford: November 23, 1997 through April 4, 1998; Kaiser: December 21, 1997 through March 7, 1998. Influenza vaccination status was ascertained from the computerized data bases of each plan.

Primary outcome measure

Excess hospitalizations and deaths during influenza seasons are strongly and linearly correlated.[25] As others have done,[26] we used as our primary study outcome the combined outcome of a hospitalization for pneumonia or influenza (P & I, ICD9-CM codes 480 - 487) or death. We used this combined outcome to enhance the power of our study and to provide more precise estimates of vaccine effectiveness within the disease-based high-risk subgroups.

Data analysis

Each participating health plan center extracted data of eligible subjects from their linked databases and forwarded these data to the coordinating data management center at HealthPartners. With EPI-Info, version 6, (CDC, Atlanta, Georgia, USA) we estimated that a minimal cohort size of 27,000 would give us an 85% chance of detecting a reduction of at least 20 percent in outcome events among recipients of the influenza vaccine. For this calculation we assumed an immunization rate of 55%, an event rate of 3% and a two-sided alpha level of 0.05. Bivariate analysis using SPSS for Windows, version 9.0, (SPSS Inc., Chicago, Illinois, USA) included Student T-tests for continuous and chi-square tests for categorical variables to test for differences between comparison groups. Multivariable logistic regression was used to assess the association of vaccination status with the study outcome measures while controlling for age, gender, co-morbid medical conditions, prior health care use (hospitalizations and outpatient visits) and whether the person had previously been hospitalized for pneumonia and influenza. In addition, site was also included in the models. For analyses according to specific subgroups, the relevant underlying medical conditions were excluded from the model. Adjusted odds ratio's (OR) and their 95% confidence intervals (95% CI) as approximations of relative risks were calculated. Vaccine effectiveness (VE) was determined as 1- OR times 100 percent. Absolute risk reductions per 1,000 vaccinees (ARR) were calculated as the vaccine effectiveness (VE) times the outcome rate in unvaccinated persons. The number needed to treat (i.e. vaccinate) to save 1 outcome (NNT) was calculated as (1/ARR)*1000.[27]

Results

Data on 122,974 and 158,454 seniors were captured for the 1996-97 and 1997-98 study years, respectively. The vaccination rates for all three sites combined were 57.7% in year 1 and 58.1% in year 2. For both years, vaccinated subjects were somewhat older and generally more likely to have high risk medical conditions than were unvaccinated subjects. (table 1) Vaccinated persons also had higher numbers of outpatient visits during the baseline period. Both groups had similar rates of hospitalization during the baseline period.

There were 1961 outcome events (hospitalizations for pneumonia or influenza or deaths) in year 1 and 2555 outcome events in year 2 (table 2). Unvaccinated persons had higher event rates than vaccinated persons in each subgroup and for both years. Vaccination was associated with a reduction in

Table 1. Baseline characteristics of study subjects by year*

	1996-97 (N = 122,974)			1997-98 (N = 158,454)		
	Vaccinated n = 71,005	**Unvaccinated n = 51,969**	**P Value**	**Vaccinated n = 92,001**	**Unvaccinated n = 66,453**	**P Value**
Mean age (SD)	74.2 (6.3)	74.0 (6.9)	<0.001	74.3 (6.4)	73.9 (6.8)	<0.001
Female sex	56.0%	58.9%	<0.001	56.0%	59.7%	<0.001
High risk	46.9%	40.7%	<0.001	62.9%	51.1%	<0.001
Heart & lung disease	7.2%	6.1%	<0.001	12.7%	10.5%	<0.001
Lung disease	16.0%	13.0%	<0.001	28.0%	22.3%	<0.001
Heart disease	27.7%	24.2%	<0.001	33.8%	27.6%	<0.001
Diabetes	13.2%	10.6%	<0.001	15.2%	12.1%	<0.001
Immune suppresssion	6.0%	5.5%	<0.001	18.5%	14.0%	<0.001
Other comorbid conditions	5.0%	6.3%	<0.001	5.7%	5.8%	0.23
Number of hospitalizations during 12 month baseline period (SD)	0.21 (0.60)	0.12 (0.65)	0.91	0.22 (0.62)	0.22 (0.68)	0.44
Number of outpatient visits during 12 month baseline period (SD)	10.02 (12.13)	9.23 (14.93)	<0.001	13.49 (14.77)	10.87 (17.02)	<0.001
Having had a hospitalization for pneumonia or influenza during 12 month baseline period	1.0%	1.1%	0.07	0.8%	0.8%	0.94

* Shown are data pooled for the three sites. High risk denotes having at least one of the following comorbid conditions listed as an outpatient or inpatient diagnosis during the 12 month baseline period: heart disease, lung disease, diabetes, immune suppression (having renal disease, hematologic or non-hematologic cancer or solid organ transplant) or other comorbid conditions (dementia/stroke, vasculitis or rheumatologic disease). SD denotes standard deviation.

Table 2. Numbers of outcome events among vaccinated and unvaccinated study subjects*

Risk Group	Season 1996-97 Number of Outcomes	Risk Group	Season 1997-98 Number of Outcomes
All		All	
vaccinated (n = 71,005)	896 (1.3%)	vaccinated (n = 92,001)	1293 (1.4%)
unvaccinated (n = 51,969)	1065 (2.0%)	unvaccinated (n = 66,453)	1262 (1.9%)
Healthy		Healthy	
vaccinated (n = 37,693)	201 (0.5%)	vaccinated (n = 34,155)	164 (0.5%)
unvaccinated (n = 30,843)	254 (0.8%)	unvaccinated (n = 32,489)	267 (0.8%)
High risk		High risk	
vaccinated (n = 33,312)	695 (2.1%)	vaccinated (n = 57,846)	1129 (2.0%)
unvaccinated (n = 21,126)	811 (3.8%)	unvaccinated (n = 33,964)	995 (2.6%)
Having heart & lung disease		Having heart & lung disease	
vaccinated (n = 5112)	229 (4.5%)	vaccinated (n = 11,728)	423 (3.6%)
unvaccinated (n = 3173)	262 (8.3%)	unvaccinated (n = 6,984)	394 (5.6%)
Lung disease		Lung disease	
vaccinated (n = 11,377)	344 (3.0%)	vaccinated (n = 25,727)	645 (2.5%)
unvaccinated (n = 6737)	388 (5.8%)	unvaccinated (n = 14,842)	555 (3.7%)
Heart disease		Heart disease	
vaccinated (n = 19,639)	471 (2.4%)	vaccinated (n = 31,094)	743 (2.4%)
unvaccinated (n = 12,596)	548 (4.4%)	unvaccinated (n = 18,350)	661 (3.6%)
Diabetes		Diabetes	
vaccinated (n = 9390)	185 (2.0%)	vaccinated (n = 13,966)	323 (2.3%)
unvaccinated (n = 5525)	197 (3.6%)	unvaccinated (n = 8,025)	255 (3.2%)
Immune suppression		Immune suppression	
vaccinated (n = 4281)	214 (5.0%)	vaccinated (n = 17,055)	484 (2.8%)
unvaccinated (n = 2882)	247 (8.6%)	unvaccinated (n = 9,287)	477 (3.2%)
Having other comorbid conditions		Having other comorbid conditions	
vaccinated (n = 3531)	107 (3.0%)	vaccinated (n = 5,230)	119 (2.3%)
unvaccinated (n = 3278)	228 (7.0%)	unvaccinated (n = 3,872)	174 (4.5%)

*High risk denotes having at least one of the following comorbid conditions listed as an outpatient or inpatient diagnosis during the 12 month baseline period: heart disease, lung disease, diabetes, immune suppression (having renal disease, hematologic or non-hematologic cancer or solid organ transplant) or other comorbid contitions (dementia/stroke, vasculitis or rheumatologic disease).

Table 3. Effectiveness of influenza vaccination in reducing the risk of hospitalization for pneumonia and influenza or death from all causes*

	1996-97		1997-98	
Risk Group	**Vaccine Effectiveness (95% CI)**	**P Value**	**Vaccine Effectiveness (95% CI)**	**P Value**
All	48% (42% to 52%)	<0.001	31% (26% to 37%)	<0.001
Healthy	46% (34% to 56%)	<0.001	42% (28% to 52%)	<0.001
High risk	47% (40% to 53%)	<0.001	29% (22% to 35%)	<0.001
Having heart & lung disease	47% (35% to 57%)	<0.001	28% (17% to 38%)	<0.001
Lung disease	48% (38% to 56%)	<0.001	27% (18% to 36%)	<0.001
Heart disease	49% (42% to 56%)	<0.001	30% (21% to 37%)	<0.001
Diabetes	50% (37% to 60%)	<0.001	21% (6% to 34%)	0.009
Immune suppression	43% (30% to 53%)	<0.001	39% (30% to 47%)	<0.001
Other comorbid conditions	56% (44% to 66%)	<0.001	39% (24% to 51%)	<0.001

*High risk denotes having at least one of the following comorbid conditions listed as an outpatient or inpatient diagnosis during the 12 month baseline period: heart disease, lung disease, diabetes, immune suppression (having renal disease, hematologic or non-hematologic cancer or solid organ transplant) or other comorbid contitions (dementia/stroke, vasculitis or rheumatologic disease). CI denotes confidence interval.

Table 4. Absolute risk reductions associated with vaccination and corresponding numbers of persons needed to vaccinate to prevent one outcome*

Risk Group	1996-97 Event rate per 1000 unvaccinated persons	Absolute risk reduction per 1000 persons vaccinated	Numbers needed to vaccinate to prevent one outcome	1997-98 Event rate among unvaccinated persons	Absolute reduction with vaccination	Numbers needed to vaccinate to prevent one outcome
All	20.5	9.8	102	19.0	5.9	170
Healthy	8.2	3.8	264	8.2	3.5	290
High Risk	38.4	18.0	55	29.3	8.5	118
Having heart & lung disease	82.6	38.8	26	56.4	15.8	63
Lung disease	57.6	27.6	35	37.4	10.1	99
Heart disease	43.5	21.3	47	36.0	10.8	93
Diabetes	35.7	17.8	56	31.8	6.7	150
Immune suppression	85.7	36.9	27	51.4	20.0	50
Having other comorbid conditions	69.6	39.0	26	44.9	17.5	57

* The absolute risk reduction per 1000 persons vaccinated = (event rate in unvaccinated persons) * (vaccine effectiveness [table 3]). The numbers need to vaccinate to prevent one outcome = (1/absolute risk reduction)*1000. High risk denotes having at least one of the following comorbid conditions listed as an outpatient or inpatient diagnosis during the 12 month baseline period: heart disease, lung disease, diabetes, immune suppression (having renal disease, hematologic or non-hematologic cancer or solid organ transplant) or other comorbid contitions (dementia/stroke, vasculitis or rheumatologic disease).

Figure 1a. Influenza Vaccine Effectiveness 1996-97

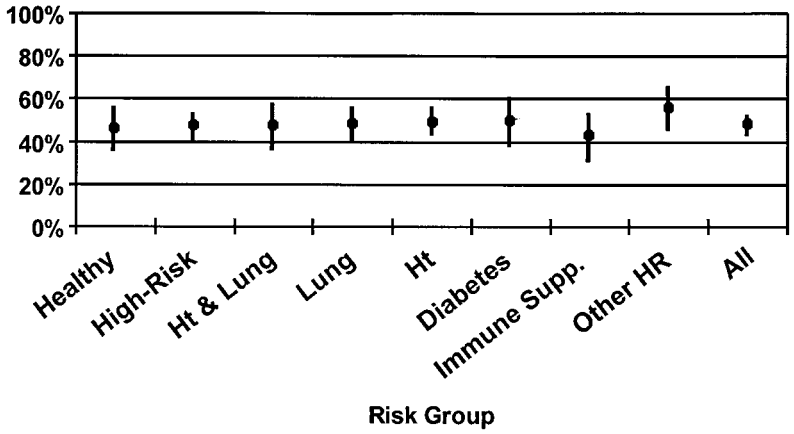
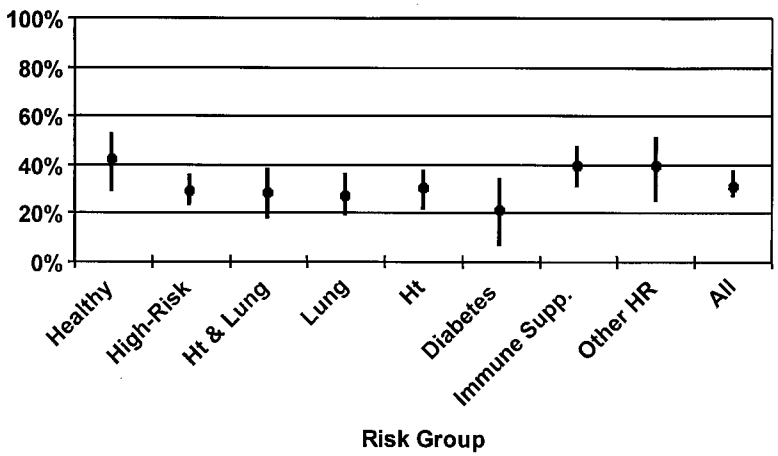


Figure 1b. Influenza Vaccine Effectiveness 1997-98



the combined outcome of a P & I hospitalization or death from any cause of 48% (95% CI 42% -52%) in year 1 and 31% (95% CI 26% to 37%) in year 2 (table 3). When analyzed according to subgroup, influenza vaccination was consistently effective across each of the disease-specific categories in both years as well as among the healthy subgroup (table 3, figure 1a & 1b).

As expected, the absolute benefits of vaccination varied by subgroup (table 4). Among healthy persons, 3.8/1,000 healthy persons were saved from hospitalization for pneumonia and influenza or death with vaccination whereas vaccination prevented 18.0/1,000 elderly with high risk medical conditions from experiencing one of these complications during year 1. Findings in year 2 were similar with an absolute risk reduction of 3.5 per 1,000 healthy elderly persons and 8.5 per 1,000 high risk elderly persons. The numbers needed to treat to prevent one outcome also reflect the higher level of absolute benefits experienced by the high-risk subgroups. In year 1, 26 to 56 persons in the various high-risk subgroups would have to be vaccinated in order to prevent one outcome while 264 healthy persons would have to be vaccinated in order to prevent one outcome (table 4). In year 2, the NNT's were 50 to 150 among persons in the high-risk subgroups and 290 for healthy persons (table 4).

Discussion

This study is unique in that the size of the cohorts allowed us to obtain precise estimates of clinical influenza vaccine effectiveness across different high-risk subgroups of seniors and to demonstrate the consistency of vaccine effectiveness across the specific risk groups. Our results also demonstrate that rates of hospitalization for pneumonia and influenza or death were highest among unvaccinated persons with high risk conditions including heart and lung disease and those with immune suppression and lowest in seniors without high-risk medical conditions which is in accordance with other studies.[3-7, 16] Thus, the absolute benefits from vaccination were highest among the high risk seniors. Nevertheless, vaccination provided benefits in all of the subgroups including the healthy elderly with reductions in risk for hospitalization or death of 9.8 events per 1,000 vaccinated persons in year 1 and 5.9 events per 1,000 vaccinated persons in year 2.

Previous studies of the benefits of influenza vaccination among elderly persons with chronic lung disease have also shown significant benefits with vaccination. Hak et al.[28] found that influenza vaccination was associated with a 50% reduction in influenza associated complications including pneumonia, cardiac disease or death among such patients. Vaccine effectivenss was even higher at 80% among persons who also had pre-exsisting cardiovascular disease. Nichol et al.[29] found that influenza vaccination of elderly persons with chronic lung disease was also highly beneficial. Vaccination in that study was associated with a 52% reducation in hospitalizations for pneumonia and influenza and a 70%

reduction in deaths. Since a recent randomized controlled trial showed that the risk of pulmonary complications resulting from vaccination is, althoug present, relatively small among adult asthmatics,[30] these results clearly support a vaccination policy for these patients.

Persons in our study with immune suppression who were vaccinated experienced substantially fewer influenza-associated complications than did their non-immunized counterparts. This is in agreement with results of a recent sero-conversion study among patients with lung cancer[31] and a randomized controlled trial of influenza vaccine effectiveness among HIV-infected persons.[32] In the latter study, vaccine recipients had no influenza infection whereas 25% of the saline placebo recipients attracted influenza: a protective efficacy of 100% (95% CI 73-100%).

Diabetics are also at higher risk for serious complications from influenza and benefitted from vaccination. Colquhoun and colleagues performed a case-control study among diabetics and estimated that influenza vaccination reduced hospital admissions for influenza, pneumonia or diabetic events by 79%.[33] US data from the Behavioral Risk Factor Surveillance System showed that most states would not reach the objective for 2000 to increase immunization rates >60% in these patients.[34] Our finding support additional immunization efforts for these groups.

Govaert et al. randomly allocated 1,838 healthy elderly persons to influenza vaccine or placebo.[15] The incidence of clinical influenza infection was 20 and 30 per 1,000 in vaccinees and non-vaccinees, respectively and the vaccine effectiveness was 47%. The absolute reduction in risk was 10 influenza cases per 1,000 vaccinated persons, a finding of unclear clinical meaning because the outcome included both mild and severe influenza illnesses but did not include influenza-associated complications. However, we have shown that an absolute reduction in serious outcomes of 3.5 to 3.8 per 1,000 healthy elderly persons can be attained which highlights the importance and potential benefits of immunization even for low risk seniors.

Even during the second year of the study when there was a poor match between the predominant circulating virus (A/Sydney/H3N2) and the corresponding vaccine strain,[24] we demonstrated a significant level of vaccine effectiveness in all of the subgroups we studied, although the level observed was somewhat lower than seen in the first year of the study. This finding suggests that there was some degree of cross protection afforded by the vaccine. Varying levels of cross protection have been observed in other studies conducted during years when there is a poor vaccine - circulating virus strain match.[35]

Several limitations of this study deserve comment. The use of a non-experimental study design may result in the potential incomparability of prognosis among vaccinees and non-vaccinees.[22] Confounding may have led to unequal balance of average risk of outcomes between the comparison groups. We were able to capture data on co-morbidity, age, gender and baseline health care use, and adjusted for their presence in the analyses. Nevertheless, our results should be interpreted with some caution.

Misclassification of vaccination status may have occurred in this study, most likely due to failure to capture vaccination status. If such misclassification were substantial, this likely would have biased the study findings to lower vaccine effectiveness rates. However, data were available from two health plans which suggest that misclassification of vaccination status was probably minimal. Data from a member survey conducted in 1995 for HealthPartners show that more than 95% of the plan seniors who were vaccinated reported receiving their influenza vaccinations at a health plan site[36] and that agreement between medical records and the computerized data bases is in excess of 90% for vaccination status.[16] Likewise, the results from annual membership surveys conducted from 1990 through 1995 at Kaiser-Permanente indicate that over 90% of elderly plan members who were immunized received their vaccine at a health plan site. Furthermore, chart audits from the plan indicate that over 98% of influenza vaccinations are recorded in their computerized database. (J Mullooly, PhD, personal communication, 1/2001).

We did not include other outcomes associated with influenza infections such as acute respiratory or cardiac disease or diabetes events leading to clinic visits or hospitalizations.[2,4,7,16] We limited our analysis to the serious influenza associated outcomes of P & I hospitalization and all-cause death because the attributable fraction due to influenza infections is relatively high during influenza seasons.[1] However, the overall absolute health benefits of vaccination might have been underestimated.[4,7,16]

We lacked information on pneumococcal vaccination status. In a recent cohort study among elderly persons with chronic pulmonary disease, two-thirds of patients had received this vaccine.[37] Results showed that reductions associated with pneumococcal vaccination were additive to those of influenza vaccination. However, it is unclear how this might have affected the estimates for effectiveness in other subgroups.[38]

It often takes an enormous effort to increase influenza vaccination coverage in a large-scale prevention program despite the fact that the vaccine is inexpensive,

well-tolerated and effective. Health policy makers, physicians and patients need valid and precise information to justify ongoing support of such strategies. This type of evidence is also helpful in identifying highest priority groups for vaccination when there is a delay or shortage of vaccine supplies as is the case in the US for the 2000-2001 season.[20,21] In case of an influenza pandemic a substantial shortfall of vaccine will likely occur as well and such information will undoubtedly be of use in that event.

Our data support current age-based recommendations for the immunization of all persons aged 65 years and older.[39] Both healthy and high-risk seniors enjoy substantial benefits from vaccination, and age-based strategies have been more effective than risk condition-based vaccination strategies in achieving high vaccination rates.[40] However, our findings also highlight the fact that elderly with underlying medical conditions do have significantly higher rates of hospitalization and death, and therefore the absolute reduction in outcomes per 1,000 vaccinated persons is higher in these groups. Thus, while all persons 65 years or older benefit from vaccination and should be targeted for annual immunization, efforts should be renewed especially to ensure vaccination among those with cardiopulmonary disease, diabetes, cancer, transplants or immune-deficiency, and other high-risk conditions.

Acknowledgment

This project was funded and sponsored by the National Vaccine Program Office and the Centers for Disease Control and Prevention, Atlanta, GA through an agreement with the American Association of Health Plans. Mr. Hak's participation was supported by a grant from the Dutch Asthma Foundation, Leusden, the Netherlands.

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CHAPTER 9

Population-based prevention of influenza in Dutch general practice

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Population-based prevention of influenza in Dutch general practice

Background Although the effectiveness of influenza vaccination in high-risk groups has been proven, vaccine coverage continues to be less than 50% in The Netherlands. To improve vaccination rates, data on the organizational factors, which should be targeted in population-based prevention of influenza, is essential.

Aim To assess the organizational factors in Dutch general practice, which were associated with the influenza vaccination rate in 1994.

Method A retrospective questionnaire study was undertaken in 1586 of the 4758 Dutch general practices, which were randomly selected. A total of 1251 (79%) practices returned a questionnaire. The items verified were practice profile, urbanization, delegation index, use of computer-based patient records, influenza vaccination characteristics and influenza vaccination rate.

Results No differences were found with regard to the percentage of single-handed practices (65%), practices situated in urban areas (38%), practices with a pharmacy (12%), patients insured by the National Health Service (59%), and use of computer-based patient records (57%) when compared with national statistics. The mean overall influenza vaccination rate was 9.0% (SD 4.0%). -Using a logistic regression analysis, a high vaccination rate (≥ 9%) was associated with the use of personal reminders (Odds Ratio (OR) 1.7, 95% confidence interval 1.3-2.2), monitoring patient compliance (OR 1.8, 1.3-2.4), marking risk patients in computer-based patient records (OR 1.3, 1.0-1.6), a small number of patients per full-time practice assistant (OR 1.5, 1.1-1.9), urban areas (OR 1.6, 1.3-2.1), and single-handed practices (OR 1.5, 1.1-1.9).

Conclusions Improvement of vaccination rates in high-risk patients may be achievable by promoting the use of personal reminders and computer-based patient records, as well as monitoring patient compliance. In addition, the role of practice assistants with regard to preventive activities should be developed further. Practices situated in rural areas and group practices may need more support with a population-based approach for the prevention of influenza.

Key words: Immunization, influenza, preventive medicine, general practice.

Published as: Hak E, Hermens RPMG, Essen GA van, Kuyvenhoven MM, Melker RA de. Population-based prevention of influenza in Dutch general Practice. *Br J Gen Pract* 1997;**47**:363-366

Influenza epidemics continue to be a major cause of excess winter morbidity and mortality.[1-4] Immunization against influenza has been proved to be effective in reducing serious complications in high-risk patients.[5-7] As a result, attempts are being made to improve vaccination rates in these patients in many countries, including the Netherlands.[8-11]

In the Netherlands and the UK, influenza vaccination is a major task of general practitioners (GPs). General practices are the site of first contact for most medical conditions and GPs have access to clinical data to identify risk patients.[12,13] However, not until the influenza guidelines for GPs were issued, together with a national influenza vaccination promotion campaign in September 1993, was an improvement in vaccination rates among Dutch high-risk patients noticeable.[14,15] Even so, only about 45% of the high-risk patients with diabetes mellitus, chronic lung disease, cardiac disease, chronic renal insufficiency, chronic staphyloccocal infection, or immunosuppression were offered vaccines in 1994.

In 1995, the Dutch Minister of Health, the National Association of GPs and the Dutch College of GPs reached an agreement on strengthening the role of GPs in population-based prevention, imitating policy changes in the UK with regard to prevention in general practice.[16] To carry out population-based prevention in general, the practice needs to be organized in such a way that patients can be traced, given the intervention and monitored efficiently.[17] To our knowledge, no studies have assessed which of the many different aspects of general practice organization should be developed so that the vaccination rate is improved. Therefore, the aim of this study was to assess which organizational factors of Dutch general practice were associated with the influenza vaccination rate in 1994.

Methods

Study population

In September 1995, a retrospective questionnaire study was conducted in one third of all 4758 general practices in the Netherlands. The computerized random selection of practice addresses was carried out by the Netherlands Institute of Primary Health Care (NIVEL). The NIVEL supplied the Department with the name and address of one GP per practice.

Items collected and definitions

Over 28 items of information were collected from each practice, including GP and practice characteristics, urbanization, patients' health insurance, delegation index, use of computer-based patient records, influenza vaccination characteristics and the number of vaccinees in 1994. In order to calculate the number of patients per full-time GP (FTGP) or practice assistant (FTPA), working hours were standardized to a full-time job. The delegation index was

based on the degree of delegation of the following activities by GPs to PAs: venous blood sampling, removing stitches, removing ear wax, measuring blood pressure, and freezing warts. The degree of delegation of each activity ranged from never (1 point) to always (5 points-). The delegation index was given by the total sum score of the degree of delegation of all five activities, ranging from 0 to 25 points.[18] A higher sum score meant more delegation of these activities to PAs.

In the Netherlands, as in many other countries, healthy persons residing in retirement/nursing homes and the elderly in general are encouraged to receive vaccinations.[19] Since, according to the influenza guidelines, risk groups should be reminded (preferably in writing) of the effects of vaccination,[14] GPs were also asked whether these two groups of elderly subjects were offered vaccines in writing. The influenza vaccination rate was calculated as the number of all vaccinees divided by the total practice population.

Statistical analysis

The outcome measurement was defined as a high or low vaccination rate using the mean vaccination rate. In the uni- and multivariate analyses, the practice setting was dichotomized into single-handed or duo/group practice, the type of invitation made offering vaccination, i.e. in writing or not, and the person who vaccinated the patient with or without a PA. Significance of differences in means or medians of characteristics between practices with high and low vaccination rate was tested with Student's t-tests or Mann-Whitney U-tests; differences in pro-portions were tested using the Pearson chi square (χ^2) test. P-values given are two-sided.

In the multivariate logistic regression analysis, only those independent variables were included that were associated ($p<0.10$) with the outcome measurement in the uni-variate analyses. The likelihood ratio statistic (LRS) was used to test for improvement of the model.[20] Effect modification was excluded by assessing the statistical significance of added inter-action terms in the model. Adjusted odds ratios (ORs) and 95% confidence intervals (95% CI) are given.

Results

Of the 1586 questionnaires sent out, 1251 (79%) were completed and returned. No substantial differences were found with regard to the percentage of single-handed practices, practices situated in urban areas, practices with a pharmacy,

percentage of patients insured by the National Health Service and the use of computer-based patient records when compared with national statistics (table 1). A full-time PA provided health care to about 450 more patients on average than a full-time GP. No national statistics were available concerning either the number of patients per full-time PA or GP, or the delegation index.

The organization of the vaccination program is given in table 2. Of the 287 practices that did not inform patients about vaccinations, eight did not vaccinate any patients (not included in table). Practices that sent personal reminders (490) most frequently, invited patients with diabetes mellitus, lung disease, or cardiac disease (>98%), whereas patients with chronic renal insufficiency (82%), chronic staphylococcal infection (78%), or immunosuppression (51%), patients in retirement/nursing homes (59%) and healthy elderly subjects (32%) were invited less often (not included in table). Few practices (209) actively monitored patient compliance and reinvited non-compliers by telephone or letter.

Table 1. Practice characteristics of the study sample, and the Netherlands as a whole. Values are numbers (%) unless stated otherwise.

Characteristic	**Study sample (N=1251)**		**the Netherlands (N=4758*)**	
Practice setting				
Single-handed	817	(65)	3322	(70)
Duo	336	(27)	1050	(22)
Group	93	(8)	386	(8)
Urban area†	477	(38)	1913	(40)
Practice with pharmacy	150	(12)	640	(13)
Computer-based patient records	717	(59)	2855	(60)
% of NHS patients‡	59%		60%	
Mean number of patients/FTPA¶ (SD)	2970 (1317)		-	
Mean number of patients/FTGP¶ (SD)	2520 (546)		-	
Low delegation index (≤10)**	556 (44)		-	

Values are numbers (%) unless stated otherwise. * Statistics provided by the NIVEL. † Urban is ≥50 000 inhabitants. Values were missing for 34 practices. ‡ Compulsory insurance for patients earning less than £21,500 (15 missing values).[26] ¶ FTPA, full-time PA (81 missing values), FTGP: full-time general practitioner (21 missing values). ** Low: a delegation index of less than 10 points indicated almost no delegation of all five tasks to PAs in general (including practices without PA, n=43).

Table 2. Organisational characteristics of the influenza vaccination programme in the study sample (N=1251)

Characteristic	Number	(%)
Invitation		
Personal reminder	490	(39)
By phone (occasionally)	216	(17)
Mass media	250	(20)
No invitation	287	(23)
Selection of risk patients*		
Tagging in CBPR	642	(51)
Selection list	641	(51)
Tagging on consultancy card	235	(19)
Vaccination in groups	877	(70)
Vaccine supply		
In practice	786	(63)
Pharmacy	454	(36)
Vaccination person		
PA with or without GP	832	(67)
GP only	349	(28)
Vaccination team	47	(4)
Monitoring compliance and reinviting	209	(17)

* More than one selection method could be present (total percentage>100%); CBPR, computer-based patient records

Overall, a mean vaccination rate of 9.0% (SD 4.0%, 25th percentile 6.2%, 75th percentile 11.2%) was reported. In univariate analyses, a high vaccination rate (more than 9%) was associated with sending personal reminders (χ^2=20.6, p<0.001), monitoring and re-inviting non-compliers (χ^2=13.2, p<0.001), tagging patients in computer-based patient records (χ^2=9.0, p<0.001), a low number of patients per full-time PA (mean 2823 v. 3055 patients, t-value=3.95, p<0.001), an urban setting (χ^2=16.0, p<.001) and a single-handed practice (χ^2=11.2, p=0.0008). The variables practice with a pharmacy, delegation index, vaccine supply, and group vaccination did not appear to be associated with the outcome measurement.

All organizational factors found in the univariate analyses were independently associated with the vaccination rate in the multivariate logistic regression

Table 3. Organisational factors associated with the vaccination rate: results of multivariate logistic regression analysis (N=1087).★ Values are numbers (percentage) unless stated otherwise

Organisational factor	Low rate (<9%)	High rate (≥9%)	Adjusted OR (95% CI)	Difference in mean vaccination rate†
Reminder‡	213/635 (34)	250/537 (47)	1.7 (1.3-2.2)	1.3
Monitoring/reinviting§	86/632 (14)	116/535 (22)	1.8 (1.3-2.4)	1.3
Tagging patients in CBPR¶	306/631 (48)	305/532 (57)	1.3 (1.0-1.6)	0.8
Low number of patients/FTPA★★	324/594 (55)	334/513 (65)	1.5 (1.1-1.9)	0.6
Urban area††	208/636 (33)	238/540 (44)	1.6 (1.3-2.1)	0.7
Single-handed★‡‡	394/635 (62)	385/540 (71)	1.5 (1.1-1.9)	0.6

Values are numbers (percentage) unless stated otherwise.
★ Reference: low vaccination rate (<9%); values for the vaccination rate (75) and user variables were missing for 164 practices. LRS of the final model: 77.1, p<0.001. † Absolute difference in mean rates (%) between the two levels of the organizational factors. ‡ Versus no personal reminder. § Versus no re-invitation of non-compliers. ¶ Versus no tagging in computer-based patient records. ★★ Versus high number (≥2970) of patients per full-time PA. †† Versus rural area (<50,000 inhabitants). ★‡‡ Versus duo or group practice

analysis (table 3). The absolute difference in mean rates between practices that sent a personal reminder or actively monitored and re-invited non-compliers (9.7%, 10.0%), and those that did not (8.4%, 8.7%) appeared most relevant.

Discussion

A population-based approach towards the prevention of influenza was practiced by only a minority of Dutch general practices in 1994. The results of this study show that sending personal reminders, monitoring and re-inviting non-compliers, using computer-based patient records for the selection of high-risk patients and having enough time available for PAs should be part of such an approach. These identified measures may equally improve uptake of preventive activities other than immunization, such as cervical or breast cancer screening.

The overall vaccination rate, as used in our study, may not accurately reflect the rate in high-risk patients. We were not able to obtain information from 1251 practices on age structure and high-risk patients listed because of a lack of full age and disease registers. Since in the Netherlands in 1994/95, vaccination was mainly limited to high-risk patients, extrapolation of the given rate will only modestly overestimate the absolute numbers of high-risk patients vaccinated at the national level.[17] Furthermore, there is no evidence of certain groups of practices with different age structure, which might explain the associations between established measures and the vaccination rate. In the Netherlands, a 1.3% higher mean vaccination rate, as found in practices that sent reminders or actively monitored patient compliance would equate with approximately 195,000 vaccinated high-risk patients at the national level. This result confirms earlier evidence of the efficacy of postal reminders and monitoring in targeting the population at risk.[4,21-23] Since only 40% of the practices complied with the influenza guideline of sending personal reminders, some recommended patient groups were barely approached. Also, an active attitude towards non-compliers was practiced by less than one fifth of the practices. These aspects should therefore be developed in strategies for improving population-based influenza prevention.

Despite the fact that the practice budget should be sufficient to employ a full-time PA in a full-time practice, this was often not the case. Dutch PAs (clergies) are in between a practice nurse and a secretary. Tasks that may be carried out by PAs include medical-technical, such as taking blood pressure or immunizing, as mentioned in our delegation index, or secretarial-like administration or intake appointments. It was surprising to find no association between the degree of delegation and vaccination rate. In the study of Nijland et al.,[18] a high association between the number of PAs (fulltime equivalents) and the delegation index was reported, which would also suggest that only the available time for the organization of the vaccination might have been most important. We did not include other possible determinants of workload, since no such information is currently available in the Netherlands. However, we suppose that the organizational competence of GPs to delegate tasks to PAs may be considered the main determinant. Thus, increasing awareness of the preventive activities that assistants can perform and the prerequisite of sufficient time available for these activities is urgently needed.

The use of computer-based patient records is financially supported by the Dutch Government and has grown exponentially over the past few years.[24] These records can supply GPs with useful information about their patients and can facilitate the tracing and monitoring of risk patients.[1,24,25] Recently, an

influenza software module, that runs through the records upon installation and selects risk patients based on diagnosis, medication or tags, was developed by software-providing companies of GP information systems. This influenza module, together with the continued use of computer-based patient records should therefore be promoted.

A higher vaccination rate in practices situated in urban areas may be the result of the support of other health organizations. In most cities with over 50 000 citizens, a so-called health authority is present. These organizations aim to improve the health of citizens and are involved with several preventive activities. Also, many patient organizations or groups supporting the elderly are mainly present in urban areas. Finally, it is difficult to find an explanation why single-handed practices performed better than group practices. Possible reasons may include: (1) the number of vaccinees in duo/group practices might have been under-reported; and (2) the organization of the vaccination program might have been more complex.

In conclusion, improvement of vaccination rates in high-risk patients, and presumably other preventive activities, may be achieved by promoting the use of personal reminders and active monitoring of patient compliance. Furthermore, the continued use of computer-based patient records in general practices should be encouraged and the role of PAs with regard to preventive activities developed further. Finally, practices situated in rural areas and group practices may need more support in a population-based approach towards the prevention of influenza.

Acknowledgements

We are thankful to the Dutch Ministry of Health for the financial support of this study. We would also like to acknowledge the Dutch College of General Practitioners (NHG) and the National Association of General Practitioners (LHV) for enabling us to conduct this study. Finally, we are grateful to Mr. A. Lodder for his useful comments on the statistical part of the study.

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CHAPTER 10

Improving influenza vaccination coverage among high-risk patients: a role for computer-supported prevention strategy?

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Improving influenza vaccination coverage among high-risk patients: a role for computer-supported prevention strategy?

Background Worldwide, population-based influenza vaccination strategies are being developed to trace, immunize and monitor high-risk persons efficiently. Computerized prevention modules may facilitate such a strategy in general practice.
Objectives We established the applicability of a computerized influenza prevention module and specifically addressed improvement of immunization coverage in high-risk patients during two consecutive influenza vaccination rounds after introduction of the module.
Methods In this descriptive study, four computerized practices of the Utrecht General Practices Network, covering about 36 000 patients, participated. In 1995, all patients with high-risk diseases were traced by relevant tags, ICPC- and ATC-codes, using the module. According to changed Dutch immunization guidelines in 1996, healthy elderly people over 65 years were also traced. Demographical and medical data included age, high-risk disease and vaccine uptake
Results In October 1995, 3871 high-risk patients were identified (11% of population); overall vaccination coverage was 68%. Over one-third of these patients had not been indicated before. In between the two vaccination rounds, 1104 previously unknown patients with high-risk diseases < 65 years were found by means of the module's online status. In October 1996, 6889 persons, including 2308 healthy elderly, were indicated (19%), and vaccination coverage was 62%.Of 3477 patients whose high-risk diseases were documented in both vaccination rounds, an overall improvement of vaccination coverage from 71% in 1995 to 76% in 1996 was observed ($P<0.05$). Main improvements were found in elderly patients. Immunization rates were highest in those with more than one risk factor, lung or cardiac disease, and lowest in healthy elderly and patients under 65 years with lung, renal, or other diseases.
Conclusion Computerized prevention modules and CMRs may facilitate population-based prevention of influenza and the use should be further encouraged.

Key words: Computer, general practice, health promotion, influenza vaccination, prevention.

Published as: Hak E, Essen GA van, Stalman WAB, Melker RA de. Improving influenza vaccination coverage among high-risk patients: a role for computer-supported prevention strategy? *Fam Pract* 1998;**15**:138-143

The yearly impact of influenza on morbidity and mortality may be considerable.[1] Immunization against influenza is effective in reducing acute complications among high-risk patients and appeared to be cost-saving among the elderly in the North American setting.[2-6] Influenza vaccination should also be regarded as one of the most cost-effective strategies compared with other preventive strategies such as hepatitis B vaccination, cervical or breast cancer screening.[7] Therefore, immunization policies have been developed so that immunization coverage in high-risk patients can be improved.[8-10]

A population-based strategy, in which the impact of preventive intervention programs can be optimized, should include tracing patients at risk, reminding by intermediaries (preferably in writing), efficiently performed preventive action(s) and monitoring patients' compliance and complications.[11,12] In countries in which primary health care is provided mainly by GPs who keep a record of the risk status of all listed patients, they are of utmost importance as intermedi-aries for such a strategy. GPs have medical information available on the majority of patients, which is essential for tracing and monitoring the target group.[13] The exponential use of computerized medical records (CMRs) in countries as The Netherlands and the UK may be considered one of the major advances in recent years with regard to population-based prevention.[14,15] In 1994, approximately 60 percent of Dutch general practices already used CMR.[11] Developed classification systems for reporting diagnoses[16] and medical treatment[17] in primary care make CMRs a useful tool for search strategies and decision-making.[18] In a recent study among a representative sample of Dutch GPs, we have shown that the use of CMRs was independently associated with a high influenza vaccination rate, apart from other organizational aspects such as sending postal reminders.[11]

In 1995, a national health promotion campaign to enhance a population-based approach towards influenza vaccination among Dutch GPs was started by the Ministry of Health, the Dutch College of General Practitioners (DCGP) and the National Association of General Practitioners. One of the aims of the campaign is to reach an immunization coverage over 70 percent for high-risk individuals in 1997. As part of this campaign, software-providing companies were asked to develop a computerized prevention module that could support the organization of the immunization program in general practices.

We aimed to evaluate the applicability of a computerized influenza prevention module during two consecutive vaccination rounds from the introduction of the module in October 1995 until December 1996 in the Utrecht Network of General Practices. Preliminary results of the use of the influenza prevention module during the 1995 vaccination round indicated high usefulness with regard to the selection, invitation, vaccination and monitoring of high-risk patients.[19] In order to gain more insights into the long-term effects of using a computer-supported prevention strategy, we specifically addressed the following research questions: (i) what was the influenza vaccination coverage in patients over and under 65 years of age of various risk-categories in 1995 and 1996; and (ii) did the immunization coverage of patients indicated in 1995 further improve in 1996?

Methods

Setting and Patients

The Utrecht Network of General Practices with six participating group practices was established in 1989 and since then all patient contacts have been registered using CMRs. Diagnoses have been classified using codes of the International Classification of Primary Care[16] according to the ICHPPC-2 criteria.[20] Medical drug prescriptions have been classified as well using the Anatomical Therapeutic Chemical (ATC) classification index.[17] In our network the focus is on an intensive contact monitoring of patient diagnoses. During the study period October 1995-December 1996, we followed the organization of two vaccination rounds in four of six network practices with 15 GPs, covering a patient population of approximately 36 000.

Until 1994, all patients at risk for influenza, according to the guidelines of the DCGP,[21] were given an influenza indication tag (IT) in the CMR only when GPs reminded themselves of indication criteria during the patient's visit. Patients with chronic lung, heart and renal disease, with diabetes mellitus, chronic staphylococcal infection and other less frequent high-risk diseases were indicated. As of October 1996, individuals over 65 years of age without documented risk factor were added to the DCGP immunization guidelines.

Functions of the computerized influenza prevention module

1. Adjustment of the DCGP Standard Selection Set with relevant tags, ICPC-, ATC-codes registered in the previous 24 months, and a computerized search for potential patients. The criterion of age over 65 years was added to the Set in 1996 (see table 1).

2. Removing patients from the list who were wrongly selected.

3. Printing a postal reminder with name and address of the selected patients.

4. Registration of the vaccination (ICPC-code R44.1).

5. On-line indication possibility for giving the influenza indication tag (IT) during the year.

6. Graphical presentation of results of all activities.

Table 1. Tags, ICPC- and ATC-codes of the DCGP Standard Set of the influenza module

Tag	relevant ICPC[a]	possibly rel. ICPC[b]	ATC[c]
CV (cardiovascular disease)	K74-K80, K82-84	K71, K73, K90, K93	C01, C02, C03, C07, B01
EN (endocarditis prophylaxis)	see CV	see CV	
LO (chronic lung disease)	R84, R85, R91, R95, R96	R70, R82, R86, R89 R99	R03
DM (diabetes mellitus)	T90	-	A10
RI (renal insufficiency)	U88, U99		
not applicable (other)	S10	B73, B74, B90, D81 L82, L85, N86, N87 N99, S99, T85, T86 T99	J01
IT (before 01/10/1995)	-	-	-
Age (65+, 1996)	-	-	-

a Relevant ICPC-codes according to DCGP guidelines:[16] B: blood, D: digestive, K: circulatory, L: musculoskeletal, N: neurological, R: respiratory, S: skin, T: endocrine and metabolic, U: urology.

b Possibly relevant ICPC-codes: see footnote a.

c C01: cardiac therapy, C02: antihypertensives, C03: diuretics, C07: b-blocking agents, B01: antithrombotics, A10: drugs used in diabetes, R03: anti-asthmatics, J01: systemic antibacterials.[17]

Computer-supported organization of the influenza vaccination

After installing the module in October 1995, a computerized search was carried out using the DCGP Standard Selection Set. All initially selected patients were automatical-ly registered by a selection tag (ST). GPs were subsequently asked to go through the printed list to verify whether a patient was rightfully selected according to GP influenza immunization guidelines.[8,21] Indicated patients were registered by an indication tag (IT) and were all sent a personal reminder for vaccination. Compliers were immunized during mass vaccination rounds in the first 2 weeks of November 1995 and registered in the CMRs. In 1996, the module was kept on-line and updated with regard to the changed guidelines in which healthy elderly (≥65 years) were indicated as well. A similar procedure for selection, reminding, vaccinating and monitoring was followed during the second vaccination round in 1996.

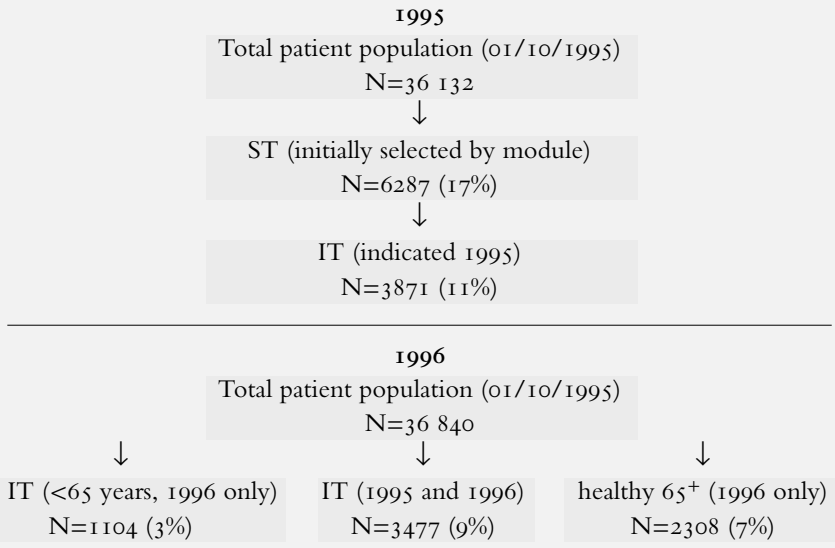
Data collection and analysis

We subdivided patients into under and over 65 years of age and constructed the following six high-risk categories according to the relevant tags, ICPC- or ATC-codes (see also table 1): patients with (i) cardiovascular disease; (ii) chronic lung disease; (iii) diabetes mellitus; (iv) renal disease; (v) other disease and (vi) more than one risk factor. We added the category healthy 65+ in the analyses concerning the second vaccination round. We used chi-square and paired proportion tests to test for statistical differences in categorical and ratio variables between two groups. Two-sided P-values <0.05 indicate statistical significance.

Results

In 1995, a total of 6287 of 36 132 patients (17%) listed in the practices were initially selected on the basis of the 1995 DCGP Standard Selection Set (see figure 1). More than half the patients (3249) were selected by an indication tag (IT) which was given manually in previous years. Others were selected by illness-specific tags (1197), medication (1141) and ICPC-codes alone (700).

Figure 1. The selection of the study populations. Absolute numbers (% of total population) are given



After checking the selection list, 773 patients were found with an IT given in previous years, but who did not require a reminder in 1995, as disease status or doctor had changed during the year.

Almost two in three initially selected patients (3871/6287) were indeed indicated for vaccination by their GP, which equals 11% of the total patient population. In all, 1395 more high-risk patients (56% increase) were found in 1995 after first use of the module, compared with the previous year. Of all patients with high-risk medical conditions, 2122 (55%) appeared to be aged under 65 years (not shown in figure 1).

In 1996, 6889 persons (19% of the patient population) were indicated for vaccination. Most of the patients with high-risk disease who were previously indicated in 1995 (3477/3871) were again registered by an IT in 1996; the remaining 394 patients were moved out of the practice or their disease status was changed. After the introduction of the on-line status of the module, an additional 1104 patients with high-risk disease aged under 65 years were found in between the two vaccination rounds. In addition, 2308 elderly without documented high-risk disease were added to the indication list. Still, more than 40% of all indicated persons appeared to be aged under 65 years (not in figure 1).

In 1995 and 1996, overall immunization rates appeared to be 68% (n=3871) and 62% (n=6889), including for the first time the 2308 healthy elderly over 65s, respectively. In both years (1995 and 1996) these rates appeared to be highest in elderly patients with more than one risk factor (78% and 82%, respectively), lung (76% and 80%) and cardiac disease (72% and 72%). Uptake was lowest in patients aged under 65 years with lung (66% and 68%), renal (65% and 72%) or other diseases such as chronic staphylococcal infection (45% and 49%). In 1996, immunization rates of healthy elderly and newly indicated patients with high-risk disease aged under 65 years (n=1104) were 43% and 62%, respectively.

In order to establish possible improvement of the immunization coverage in high-risk patients after 2 years of calling up, we showed vaccination rates of patients with high-risk disease who could be followed during two consecutive vaccination rounds (1995 and 1996) by age and risk category (see table 2). The overall vaccination rate of this patient group was 71% in 1995 and improved by 5% on average to a level of 76% in 1996 ($p<0.05$). As similarly found in the separate year cohorts, mean vaccination rates were higher in patients aged over 65 years (76 and 83%) and rates improved more pronouncedly as well compared with patients under that age (67 and 70%). Highest statistically significant improvement in vaccine uptake was found in elderly patients with cardiac

Table 2 Vaccination rates in patients followed in 1995 and 1996 by age and risk category (n=3477)

Risk status	Age category	N	Vaccination rates 1995	Vaccination rates 1996	Difference (1995-1996)
Cardiac disease	≥ 65	711	515 (72)	566 (80)[a]	8[b]
	< 65	367	257 (70)	269 (73)	3
Lung disease	≥ 65	244	195 (80)a	210 (86)[a]	6[b]
	< 65	1024	663 (65)	685 (67)	2
Diabetes mellitus	≥ 65	136	97 (71)	107 (77)	6[b]
	< 65	174	123 (71)	127 (73)	2
Renal insufficiency	≥ 65	16	8 (50)	9 (56)	6
	< 65	18	13 (72)	11 (61)	-11
Other	≥ 65	25	14 (56)	19 (76)[a]	20
	< 65	59	29 (49)	30 (51)	2
> 1 risk factors	≥ 65	500	409 (82)	435 (87)	5[b]
	< 65	203	158 (78)	167 (82)	4
Total	≥ 65	1632	1238 (76)	1346 (83)[a]	7 [b]
	< 65	1845	1243 (67)	1289 (70)	3[b]
	all ages	3477	2481 (71)	2635 (76)	5[b]

a ≥65 versus <65, chi-square P < 0.05.
b 1995 versus 1996, paired proportion test P < 0.05.

disease (8%). In patients aged under 65 years with lung, renal or other diseases and diabetes mellitus, almost no improvement was observed.

Discussion

Current information on immunization rates in various high-risk patient groups in Western countries is lacking due to incomplete registration of disease status, age and received vaccinations in primary care. This study showed that monitoring immunization rates in different disease and age categories is facilitated by using CMRs and a computerized influenza prevention module in general practice. In our network we found that about 70% of patients with high-risk disease were immunized in 1995 and vaccination coverage even improved in patients invited for the second time. The most significant improvement was found among the elderly, especially those at highest risk as

chronic lung and cardiac patients. Lower immunization rates were observed in healthy elderly and patients under 65 years invited for the first time. This confirms earlier evidence by Hutchinson et al.,[22] who observed higher uptake after repeated reminding.

These results also demonstrate that a computer-supported search strategy may greatly enhance the first step of population-based prevention, namely, the selection of high-risk patients. After the introduction of the influenza prevention module in 1995, more than twice as many patients at risk could be identified compared with the previous years. As most of the patients were selected by the use of tags and medication, the search strategy used may be of equal benefit to GPs who do not make use of coded diagnoses. Also, the on-line function enhances an active attitude towards the identification and education of high-risk patients regarding this subject.

The proportion of 11 percent of patients with high-risk disease in 1995 is in accordance with other population-based studies carried out in The Netherlands.[11,23] Owing to the inclusion of individuals aged over 65 years without documen-ted high-risk disease in 1996, this proportion of indicated patients rose to 19% of the total practice population. For a full-time working Dutch GP with a mean number of 2350 patients listed, this means a considerable number of 445 patients to be reminded and immunized on average. We found that almost four out of ten these patients appeared to be aged under 65 years. Since most cost-effectiveness studies have been carried out among elderly populations,[24] not much is known about health and economic benefits associated with immunizing younger adults with various high-risk diseases, and such studies are therefore urgently needed.[25]

The present descriptive study was not intended to be representative for the Dutch GP population. The participating GPs are part of an academic network and are well trained in classifying their patients in CMRs. However, the patient population is comparable with the Dutch population.[26] The advantage of such a setting is that it shows the ideal situation in which every GP who uses CMR and the influenza prevention module may reach immunization levels above 70%, and may be able to identify many, if not all, high-risk patients. Another limitation of the present study was the lack of a comparison group. No inferences can be made about this computerized prevention strategy being superior over another prevention strategy that already exists. However, we do believe that the high immunization coverage as observed in our study may not be reached easily without a highly sensitive search-and-monitoring facility.

In conclusion, the use of computerized prevention module may greatly facilitate population-based prevention of influenza. Advantages include an effective search for potential high-risk individuals, and automatic reminder and vaccination registration functions. The use CMRs and the influenza prevention module should therefore be encouraged on a larger scale.

Acknowledgements

We are indebted to F. Leffers, MSC, computer engineer, for help with the data collection and useful comments on the manuscript. This study was supported financially by the Dutch Council of the Sick Fund. We would like to thank the Utrecht Network of General Practices group:
HAM Asbreuk, JG Blankestijn, JG Blommestein, JF Bolderink, MW van den Broek, GJA Daggelders, MEL van Dillen, WH Eizenga, MM de Groot, EFHM Henderickx, R Hirsch, HHG de Jong, JMA Juffermans, ME Numans HM Pieters, CD Rijkens, FH Rutten, BE van der Snoek, W Stalman, Y Stoutenbeek, L Truijens, NJ de Wit, WLG van Zijl.

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CHAPTER 11

Effectiveness of a coordinated nationwide program to improve influenza immunization rates in the Netherlands

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Effectiveness of a coordinated nationwide program to improve influenza immunization rates in the Netherlands

Objective To assess the effectiveness of a nationwide multifaceted intervention program involving general practitioners (GP) on influenza immunization practice.
Design Pragmatic before-after trial using pre- and post-measurement questionnaires.
Setting and subjects Random sample of Dutch general practices.
Intervention During a 2.5-year period (1995-1997) a variety of methods was implemented to enhance physician adoption of the immunization guideline, including employment of facilitators, information-based methods, small-group consensus meetings, individual instructions and introduction of supportive computer software.
Main outcome measures Influenza immunization practice and influenza vaccine uptake.
Results In 988 practices all influenza vaccination characteristics markedly improved from 1995 to 1997. Most significant changes were found in computerized marking of high-risk patients (from 54 to 82% of practices), computerized selection (41 to 77%) and sending personal reminders (40 to 77%). Vaccine uptake increased from 9 to 16% of the practice population (78% increase, $p<.001$). Uptake was most prominent in urban and single-handed practices and those with more patients insured through the National Health Service, low GP workload and low baseline uptake.
Conclusion Our data suggest that a coordinated approach involving primary care physicians can succeed in enlarging the public health impact of a population-based preventive measure.

Key words: influenza, immunization, preventive medicine, general practice, public health.

Published as: Hak E, Hermens RPMG, Hoes AW, Verheij TJM, Kuyvenhoven MM, Essen GA van. Effectiveness of a coordinated nationwide programme to improve influenza immunization rates. *Scand J Prim Health Care* 2000;**18**:237-41

Immunization against influenza is effective in reducing excess winter morbidity and mortality during epidemics.[1] In the United States as well as in the Netherlands studies suggest that in high-risk patients this preventive measure is cost-effective as well.[2-4] Therefore, strategies are being elaborated worldwide to increase immunization levels in order to reduce the burden of influenza epidemics and to control public health care costs.[2-5]

Most efforts to increase vaccine uptake focused on a patient-based approach within clinical settings. However, since the majority of high-risk persons cannot be reached within such settings, a coordinated population-based prevention strategy involving primary care physicians has recently been advocated. [5-6] Such an efficient strategy should include optimal tracing of all

high-risk persons, written invitation by physicians, efficiently performed preventive measures and monitoring compliance of patients.

In many Western countries primary health care is mainly provided by general practitioners (GPs). These physicians keep a record of the vast majority of residents including demographic and medical information. Therefore, the involvement of GPs and adoption of GP-guidelines to ensure an efficient prevention strategy is essential.

In 1994, the Dutch Ministry of Health, the Dutch College and the National Association of GPs agreed on a prevention policy involving a major role for GPs. In a pre-measurement questionnaire survey among a random sample of GPs we demonstrated that most failed to incorporate the GP-guideline on influenza immunization procedures into practice in 1994.[7] Consequently, a nationwide collaborative prevention program was initiated in 1995 which first aimed at improving influenza vaccination in general practice. Without an effective intervention no reactive arrangements or substantial change in vaccination rates could be detected in control practices of three earlier smallscale educational studies.[6,8,9] For this reason, nationwide implementation of the coordinated prevention program enabled us to assess its effects on influenza immunization practice and overall vaccine uptake.

Material and methods

GP-guideline: influenza vaccination of high-risk persons

In short, the following steps were advocated:[10]

- Marking of high-risk persons on a list. Until 1995 indications were directed at patients with high-risk diseases such as chronic heart, lung and renal disease, diabetes, and immune dysfunction and at persons living in residential or nursing homes (12% of residents). In 1996, the Dutch College of GPs (DCGP) agreed on extending indications to all healthy persons over 65 years (19% of residents) in analogy many European countries.[5]
- Sending mail prompts.
- Organizing immunization rounds.
- Providing adequate patient information.
- Purchasing vaccines centrally. Total expenses of approximately $8 for administering the vaccine plus $3 for supplies are claimed at the National Health Service (NHS).

The Dutch collaborative prevention program

Integrating knowledge on both the baseline situation concerning general adoption of the immunization guideline and on effective educational models, a combination strategy with different methods at national, GP-district and office level was implemented (Table I).

On a national level, the use of the GP influenza guideline was advocated.[10] Furthermore, a team of experts was employed within the GP-organizations to integrate primary care procedures. Materials such as reminder cards, patient education brochures and organizational information for GPs were developed, and further financial arrangements concerning reimbursement were made.

At GP-district level (in total 23 districts with autonomous management organization), Continuing Medical Education (CME) and Small-Group (SG) consensus meetings were organized for both GPs and practice assistants. A district-coordinator was appointed to facilitate the management of preventive activities.

Facilitators were employed in each GP-districts to individually support GPs at their office to adopt the immunization guideline. Facilitating tasks included the improvement of the practice organization, assistance with using computerized registration and supportive software, assistance with coordination of task division

Table 1. Contents of the Dutch three-level coordinated prevention program

Level	Main contents	Personnel
National	- Enhancing adoption of GP-guideline on influenza and immunization - Development of educational material and patient information - Centralizing vaccine delivery - Financial arrangements - Task division of primary care organizations	Team of professionals within NAGP/DCGP[1]
GP district	- Continuing Medical Education meetings - Small-Group consensus meetings	District-coordinator/GP
GP office	- GP education and instruction	Facilitator/outreach visitor

[1] NAGP: National Association of GPs, DCGP: Dutch College of GPs.

of practice personnel and health care partners (pharmacies, etc.), and the supply of brochures. The contents of the facilitator training program— the key strategy— focused on the performance of a multifaceted outreach visit intervention.[11] Standardized activities comprised an introductory visit and practice analysis. Tailored steps included the writing of a feedback report, cooperative plan of action, implementing changes, monitoring progress and gradual withdrawal.

Study design and subjects

The evaluation study was designed as a prospective pragmatic before-after trial in a random sample of GP offices. To assess to what extent GPs had adopted the guideline on influenza vaccination at baseline (autumn 1994), we invited one in three of all 4758 Dutch GP practices to participate. Addresses were randomly sampled by computer from the Netherlands Institute of Primary Care database. Per practice, we asked one GP to fill in a pre-measurement questionnaire. The same questionnaire was sent in December 1997 to all first-round responders to establish the situation after the intervention (autumn 1997). GPs who completed a questionnaire in both survey rounds constituted the study population.

Items collected and outcome measures

The contents of the questionnaire and definitions used have been reported in depth elsewhere.[7] In short, we collected two sets of items for each practice, including baseline information on practice characteristics and urbanization as well as outcome data on the organization of influenza vaccination and vaccination rate. The primary outcome overall influenza vaccination rate was calculated as the number of all vaccinees divided by the total number of patients listed. Due to incomplete patient registers, we were not able to collect data on immunization rates in specific high-risk groups.[7]

Statistical analysis

Statistical analysis was performed using SPSS 7.0 for Windows. The unit for statistical analysis was the practice. For partnership practices all data were aggregated to practice level. We analyzed differences in influenza characteristics using the formula for the difference in paired proportions.[12] A two-sided p-value of 0.05 was considered to indicate statistical significance. Univariate analysis was carried out to detect predicting baseline variables for the increase in the primary outcome vaccination rate between 1994 and 1997 using t-tests or Mann-Whitney U tests. We applied multivariate regression analysis to assess independent effects of different predictors on the increase in vaccination rate. The F-statistic was used in a backward elimination procedure to assess statistical significance of deleting potential predictors. With standard diagnostics we assessed the accuracy of the final model and checked the assumptions.[13]

Results

Study population

The pre-measurement questionnaire was returned by 1251 GPs (79%) of the original study sample (n=1586). In 1997, 988/1251 (79%) returned the post-measurement questionnaire, resulting in an overall response rate of 62%. No major differences in baseline practice characteristics between participating practices and all Dutch practices were observed (Table 2). Nor were there any differences in these characteristics between the pre- and post measurement group (not in table).

Table 2. Baseline characteristics of participating GP practices and all Dutch practices (1994)

	Study population (n = 988) (%)	**the Netherlands (n= 4758)[1] (%)**
Practice setting		
single-handed	66	70
duo/group	34	30
Practice with pharmacy	11	13
Computer-based patient records[2]	61	60
Percentage of NHS patients[3]	61	60
Urban area[4]	38	40
Low delegation index (<10)[5]	43	NA
N patients/FTPA (mean, SD)[6]	2973 (1060)	NA
N patients/FTGP (mean, SD)[6]	2523 (534)	NA

NA Not Available.

1 Data provided by the National Institute for Primary Care.

2 Values for this variable were missing for 6 practices.

3 Compulsory insurance for patients earning less than £21 500 (30 missing values).

4 Urban: ≥50 000 inhabitants.

5 Low: a delegation index of less than 10 points indicates almost no delegation of five medical-technical activities to PAs in general (including practices without PA, n = 41).

6 FTPA: full-time practice assistant (30 missing values); FTGP: full-time general practitioner (30 missing values).

Table 3. Changes in influenza vaccination characteristics (Δ%) and mean vaccination rate in Dutch general practice before (1994) and after (1997) the intervention program.

Influenza vaccination characteristics	**1994** %	**1997** %	**1994-97** Δ% [1]
Marking high-risk persons in CBPR[2]	54	82	28
Use of computer-supported selection	41	77	36
Use of computerized influenza prevention module	-	77	-
Sending mail prompts	40	77	37
Special vaccination hours	72	86	14
Immunization by practice assistant	69	78	9
Monitoring non-compliance and reminding	19	29	11
Overall influenza vaccination rate	9.1	16.3	7.2

[1] All changes were statistically significant ($p<0.05$).
[2] CBPR: computer-based patient records.

Effects on immunization practice and vaccine uptake

Except for a substantial increase in the use of computer-based patient records (62 to 80% of practices, not in table), virtually no change in other baseline organizational characteristics of the practice could be observed between 1994 and 1997. However, as presented in table 3, major changes were found in incorporating immunization guideline procedures into practice. All relevant items improved markedly during the intervention period. Largest gains were observed in marking high-risk individuals in computer-based patient records (54 to 82% of practices), computer-supported selection (41 to 77%), sending personal reminders (40 to 77%) and use of the computerized influenza prevention module (0 to 77%). Importantly, vaccine uptake increased from 9 to 16% of the practice population (78% increase, $p<.001$). Using multivariate regression analysis, only few baseline variables statistically significantly predicted the increase in immunization rate (Table 4). In urban practices, for example, the mean increase in immunization rate between 1994 and 1997 was 8.4% as opposed to 7.2% in rural practices, whereas GPs with a high workload (high number of patients per full-time GP) recorded 0.7% less uptake than their colleagues.

Table 4. Characteristics predicting the increase in mean vaccination rate; results of the final regression model [1]

Predictors	B	SEB	p-value
Urbanization (0=rural, 1=urban)	1.15	0.25	<.001
Practice (0=duo/group, 1=single)	0.65	0.11	0.017
Workload (0 = <2577, 1 = ≥2577)[2]	-0.59	0.24	0.018
% NHS patients (continuous)	0.02	0.01	0.023
Mean vaccination rate at baseline (continuous)	-0.15	-0.24	<.001
Constant	7.15		<.001

[1] F-statistic (5,840): 12.1, p<.001; R^2 : 0.06
[2] Dichotomized using statistical mean

Discussion

These data suggest that after a 2.5-year period the collaborative program with a combination strategy was effective in improving influenza immunization practice in the Netherlands.

A limitation of our study might be the lack of a randomly allocated control group that received no intervention. Observed changes may therefore have resulted from factors other than the intervention. Since it was regarded unfeasible to withhold support of preventive activities in individual GP practices, no such comparison group was available. However, the following arguments support the conclusion that the observed improvement can be largely attributed to the intervention. First, in three comparable controlled small-scale studies aiming at improving influenza vaccination procedures, no relevant changes with regard to influenza prevention were found in the comparison group receiving no intervention.[6,8,9] Secondly, most other characteristics of the practice organization in general remained unchanged during the intervention period. Finally, an increase of only 11 percent in the monitoring/reminding of non-compliers, which was not an essential part of the intervention program (see also GP-guideline, methods), was found. This improvement is far less than observed for the immunization guideline items that were essential in the intervention program.

Our findings are consistent with that what others also have observed — succesful change of physician's behaviour through combined educational efforts.[6,8,9,14,15] The elaboration of clear guidelines for physicians and the use of a combination of appropriate methods to implement these protocols into clinical practice have proven to be essential.[16] In this study, improvement was largest in GP-activities most susceptible to gains such as sending personal and adoption of computer-based patient records to store information. Personal reminders are effective in raising vaccination levels in high-risk individuals.[14,17,18] Until recently little was known, however, about the surplus value of computerized support by specific prevention modules. The computerized influenza prevention module was developed to support the selection, reminding and monitoring of patient's compliance using available classified medical information. In a prospective study, we recorded about 40% more vaccine-eligible persons as opposed to previous years and observed immunization rates reaching 80% in high-risk persons after two years.[19] The present study shows that nationwide implementation of such a technological support system is feasible in general practice.

We demonstrated that in 1994 12 percent of all patients listed were indicated, whereas in 1997 19 percent (including healthy elderly) were indicated.[19] Since GPs are only reimbursed for immunizing indicated patients and most Dutch residents are currently listed, the presented figures can be used to calculate specific immunization rates in high-risk individuals. A 12 percent increase from 75 percent in 1994 to 84 percent in 1997 may have occurred. Despite lower specific immunization rates observed in random sample surveys of Dutch inhabitants in 1994 and 1997 (44 to 50 percent, respectively), a similar relative increase was recorded.[20] In addition, our 1997 estimate was confirmed by data of the National Information Network of General Practice (LINH).[21]

Largest increase in vaccine uptake occurred in urban and single-handed practices and those with more NHS-patients, low GP workload as well as low baseline uptake. This finding is largely in accordance with previous data.[7] We may only speculate on reasons why practices in urban areas and single-handed practices performed better. It is not inconceivable that urban practices are supported by other primary health care organizations. Furthermore, either numbers of immunizations in duo/group practices might have been underreported or implementation of the immunization guideline might have been more complex in those practices. Finally, more high-risk persons can be found among patients insured through the National Health Service than among patients with private insurance.

We could not assess the effectiveness of different elements of the intervention separately. The established high overall effectiveness of an intervention-mix with methods ranging from financial arrangements at national level to individual instructions in changing physicians' behavior is in accordance with many previous studies.[14,16]

In conclusion, the Dutch collaborative prevention project appeared successful in improving influenza immunization practice in general practice. In planning efforts to enlarge the public health impact of other preventive measures such as pneumococcal vaccination, cervical cancer screening and smoking cessation a similar variety of approaches might be appropriate.

Acknowledgment

This study was supported by a grant of the Dutch Ministry of Health, Welfare and Sports. We would like to thank the Dutch College and the National Association of General practitioners for supporting the conduct of the study. We greatly acknowledge the support on the statistical part by P. Zuithoff, statistician.

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CHAPTER 12

General Discussion

General discussion

The purpose of the studies outlined in this thesis was to add to knowledge on the prevention of morbidity and mortality from influenza. The paradigm to study effects of an intervention is the randomized controlled trial but for ethical and practical reasons inappropriate for our purposes, so we chose non-experimental study designs varying from traditional case-control (chapter 2), and cohort studies (chapters 3, 5, 6, 8) to a nested case-control study with the use of the propensity score method (chapter 7), and an uncontrolled before-and-after trial (chapter 11). In this final chapter, the main findings of our work, recommendations for clinical preventive practice and areas for future research are discussed under the headings of Prognosis of influenza, Clinical effectiveness of influenza vaccination, and Implementation of influenza vaccination.

Part I. Prognosis of influenza

The first study (chapter 2) showed that in Dutch adult high-risk patients, in whom influenza vaccination rates currently average 90 percent, non-modifiable patient factors readily assessable in primary care are associated with an increased risk of fatal or non-fatal hospital admission for influenza or its complications, particularly among patients of working-age. In the second study (chapter 3) we presented a clinical prediction rule for the probability of need for hospitalization for influenza or pneumonia, or death which we also validated in many additional cohorts. We demonstrated that application of this rule incorporating patient factors, efficiently reduces the group of elderly members of various US health maintenance organizations for whom efforts should be renewed to target them for influenza vaccination or additional care by 50 percent.

The factors we have identified allow clinicians to know which patients are at increased risk of complications from influenza. Future medical guidelines on influenza vaccination or treatment can incorporate the risk factors and scoring rule. This simple scoring list could facilitate the identification of high-risk patients in clinical practice, and specific software modules could be integrated into GP information systems to select them automatically for influenza vaccination. The scoring rule could even be made available to the general public through mass media.

We recommend additional efforts to increase compliance by such high-risk patients with annual influenza vaccination programs. In addition, prompt treatment of influenza by prescription of neuraminidase inhibitors such as

zanamivir or oseltamivir could be of value in these patients,[1,2] and the need for immediate treatment of complications such as pneumonia, congestive heart failure, or loss of control of diabetes should be emphasized. Finally, in the event of a vaccine shortage, possible in a pandemic[3], the clinical prediction rule could be used to direct preventive and therapeutic care to those who need it most. Health care authorities' plans for control of a pandemic should also incorporate such information.

Since we have demonstrated the usefulness of a clinical prediction rule among the elderly, future prognostic studies could focus on the development of similar rules for other relevant sectors of the community. The US Advisory Committee on Immunization Practices has added people aged 50—64 years to this vaccine target group,[4] one of the reasons for including them being that about a third have one or more high-risk medical conditions, but the absolute risks for the occurrence of morbidity from influenza among them, however, are unknown. Moreover, the majority of complications may very well occur in a small subsection of this group, particularly in patients with high-risk medical conditions already covered by the immunization guidelines. Another group in which the epidemiology of influenza differs considerably from that of adult patients,[4] and for whom a prediction rule could be useful, is young children with high-risk disease. Many recent vaccination studies have focused on healthy children in the community or in day-care,[5-7] in most of whom influenza, if it occurs, is uncomplicated. In contrast, as we have shown, children with asthma, for example, are at increased risk for exacerbations of their asthma due to the respiratory virus, but again, major determinants of serious complications are unknown.

Newly developed prediction rules always tend to be more accurate for the population from which they were derived than from other populations to which it may subsequently be wished to apply them.[8] For example, the number and type of risk factors and the relative influence of these factors on the incidence of serious outcomes were different in the Dutch adult population of chapter 2 and the US elderly population studied in chapter 3, as were other prognostic studies carried out in European[9,10] or US settings.[11-16] Therefore, external validation of prediction rules should be carried out in other relevant settings before being extrapolated to them.

Part II. Clinical effectiveness of influenza vaccination

In non-experimental studies evaluating the effects of interventions, 'confounding by indication' is an important type of bias that has to be eliminated.[17] In chapter 4 we have shown the results of using different study

designs and analytical techniques applied to data of chapter 6. Conventional tools such as restriction and statistical adjustment appeared to be effective in reducing confounding, provided that, as was the case in our studies, extensive prognostic information had been collected on each study patient. Since most Dutch citizens are listed with a GP, such data can be obtained by review of the computerized patient records.

One of the most prominent and effective methods to reduce confounding appears to be the design of quasi-experiments on the basis of propensity scores. The application of this method is largely dependent, however, on the size of the study population and the distribution of exposure within it. As we have shown in chapter 6, vaccination rates were high (approximately 80 percent). Since we selected a vaccinated person for each unvaccinated patient (20 percent of the full data set) with an equal probability of being vaccinated, many vaccinated persons had to be excluded from the analysis because there was no counterpart for them with similar prognosis. Another disadvantage of such quasi-experiments is the potential for residual confounding by unmeasured factors that can not be controlled for when applying either regression techniques or the propensity score method.[18]

Other promising methods to deal with 'confounding by indication' might be the use of instrumental variables[19] or the Grade Of Membership (GOM) analysis.[20] Both methods originate from the field of economics and have rarely been used in medical studies. Connors and colleagues used ZIP codes as an instrumental variable to divide those within or outside a small circle around a hospital, and such quasi-randomization resulted in exposure groups with similar prognosis —a similar distribution of health characteristics. However, it will be a challenge to identify useful instrumental variables in the Netherlands. In the 'GOM'-analysis, more specific clusters of patients are defined on the basis of patient characteristics. This method allows for establishing the effects of drugs within groups of patients with a shared health dimension. However, the development of such a multi-dimensional model requires large sample sizes and data on many health aspects.

Apart from the applied techniques, several of our studies show that the effects of adding potential additional confouders to the regression model including already some strong confounders on the effect parameter is only limited. The putative effects of an unmeasured confounder mainly depend on the expected prevalence of this unobserved variable in the study population, and its associations with both exposure and clinical end point.[18] Particularly in the absence of the measurement of well-known strong prognostic patient factors,

sensitivity analysis can be applied to show whether the inclusion of an unmeasured factor in the statistical analysis would have led to other findings.

The data from the non-experimental studies of the effectiveness of influenza vaccine described in chapters 5 to 8 of this thesis allow us to make some clinical recommendations. The occurrence of morbidity such as episodes of exacerbations of asthma, or of pneumonia or otitis media in preschool children with asthma during influenza epidemics is high, averaging 43 percent. Also, more serious complications from influenza, such as the need for hospitalization for acute respiratory disease, fatal or otherwise, are common in the elderly, particularly when they also have a high-risk chronic disease. In both such young high-risk children and in the elderly, conventional annual influenza vaccination reduces the incidence of morbidity and mortality from influenza by more than 40 percent, clearly justifying the use of prophylactic vaccination in these groups. Also, renewed efforts should be made to target categories of elderly patients in whom protective antibody response to vaccination have been reported to be suboptimal, such as patients with diabetes, cancer, or immune-deficiency or other infrequent high-risk conditions.[4]

In contrast, in schoolchildren with high-risk medical conditions and patients of working-age —most of them with asthma or COPD— serious morbidity from influenza is less common than in the high-risk subgroups at either end of the age-spectrum. Importantly, in these patients of working-age in two of our studies (chapters 6 and 7) influenza vaccination appeared not to be associated with reductions in the incidence of such morbidity. The first prospective study was small, covered only one season, and we probably adjusted its results in adequetely for confounding (odds ratio far above 1). The second study, however, had adequate power to detect a small reduction in morbidity due to the vaccine, and confounding was minimized because of the study design and statistical analysis methods used. In neither study was their any evidence of clinical benefit from influenza vaccination. In a randomized controlled trial by Nicholson et al.[21] influenza vaccination even appeared to be associated with deterioration of pulmonary function among these asthmatic patients. Since there is as yet no evidence that these negative negative effects of vaccination are outweighed by the benefits of conventional influenza vaccination,[22,23] this large group of patients of working-age needs to be excluded from routine vaccination.

Future research is needed to understand the pathological mechanisms of influenza infection in older children and adults with chronic pulmonary disease. Our study is the first to show that influenza is often associated with acute

exacerbations of asthma or COPD. The few exisiting studies on the association between viral infections and acute exacerbations of lung disease among patients of working-age had not shown such a strong association.[24-26] This might be because the conventional diagnostic tests used in them were much less accurate than our PCR analysis,[27] which should be part of future effectiveness studies, particularly when other end points than we have examined are studied. There is evidence from both animal and human experimentation to support the concept that viral respiratory infections, including influenza, cause ongoing bronchial inflammation and bronchial hyperreactivity among patients of working-age with asthma or COPD.[28,29] Therefore, studies to establish the effects of other preventive or therapeutic measures on influenza morbidity such as self-management programs aimed at reducing the occurrence of exacerbations of underlying lung disease in this particular patient group could provide a new and important step forwards in public health control of influenza.

Apart from studies on the pathology of influenza, the cost effectiveness of the Dutch primary care-based prevention program needs to be studied at the community. Postma and colleagues conducted an important modeling study to assess costs and effects of influenza vaccination in the Netherlands.[30] However, the input of the model was largely based on assumptions about the effectiveness of influenza vaccine as well as on the incidence of complications as hospitalizations for pneumonia or influenza, or death among persons recommended for vaccination. At the time of that study, most of these variables could not adequately be estimated. Our studies provide more specific input to assess costs and effects of the current influenza vaccination strategy. In particular, future studies should focus on the effects and costs of conventional influenza vaccination in specific subsections of the vaccine target group.

Influenza can predispose to secondary bacterial infections, and Streptococcus pneumoniae is one of the bacteria most frequently isolated in such infections, being found in about a third of pneumonia cases[31] and of children with otitis media acuta.[32] Specific antistreptococcal vaccines, such as conventional 23-valent polysaccharide pneumococcal vaccine for the elderly[33] or conjugated pneumococcal vaccine for high-risk children, have been developed to protect individuals against S. pneumoniae and more data are needed on the potential health benefits of these additional vaccinations.[34]

Part III. Implementation of influenza vaccination

Clinical prognostic studies provide crucial evidence on which to base preventive practice. From the studies in part I and II, and data from other study groups, it can be concluded that annual immunization against influenza has a

considerable beneficial impact on the influenza-associated burden in the elderly,[9,10,14-16] particularly among those with high-risk medical conditions and very young high-risk children.[35] However, for actual reduction of morbidity from influenza, particularly for these two high-risk groups, the current GP immunization guideline should be incorporated into preventive health care.[36] In the last part of this thesis we tried to describe the introduction and effects of current Dutch preventive practice in respect of influenza.

Since prevention programs should be targeted at those individuals most likely to benefit from vaccination and individual risks can only be estimated from medical databases with up-to-date prognostic information, general practitioners are important mediators for such programs. From the evaluation study (chapter 11) we learnt that support by regional GP management districts and involvement of facilitators are essential elements in changing preventive behavior.

In clinical preventive practice, user-friendly software modules integrated in the routine administration of primary care can facilitate many time-consuming organizational aspects of immunization practice and hence effectively enhance immunization rates (chapter 10). These findings agree with those of the few earlier studies that the presence of general practitioner information systems and facilitating software appears to improve preventive cardiovascular services[37] and cervical cancer screening.[38]

In addition, it should be recognized that practice nurses can play an important role in prevention and medical control services in the Netherlands. Another study corroborate our finding of an improved preventive service among those GPs who delegate preventive tasks to their practice assistants.[38] Many relatively uncomplicated medical tasks and administrative tasks can, as just mentioned, be delegated to trained practice assistants or nurses.

One of the major limitations of the evaluation study (chapter 11) was the absence of specific immunization rates in (subsections of) the vaccine target group. Also, no data were collected on the influenza-related morbidity and mortality, to establish a potential decrease of its burden in the Netherlands. Future studies, preferably carried out in extensive GP networks, should both monitor immunization rates and follow a potential effect of general immunization on the incidence of morbidity from influenza in the complete vaccine target group and in specific subgroups.

In many countries some patients are recommended to be vaccinated with 23-valent polysaccharide pneumococcal vaccine as well as influenza vaccine.[39] This additional vaccination has so far not been shown in the Netherlands to be cost effective,[40-43] and the effects of introducing this or other newly developed vaccines on patient adherence with immunization recommendations and the factors that affect the acceptance of the vaccines should also be studied.[44]

In conclusion

Prognostic information on influenza and its complications is essential to direct medical care and preventive measures at those who need them and such information should be incorporated into the recommendations for routine influenza immunization. Several patient factors such as advancing age, male sex, insurance through the National Health Service, presence of asthma or COPD, other co-morbidity and polypharmacy have been shown to be associated with a high probability of morbidity from influenza, particularly in patients of working-age. In planning control measures for a potential influenza pandemic, a clinical prediction rule can also be of value to set priorities for high-risk patients. Our studies of the effectiveness of influenza demonstrated health benefits for very young children with asthma, and for the elderly. Efforts should be renewed to ensure that these vulnerable patient groups are immunized against influenza. Data from two of our studies among patients of working-age with asthma or COPD showed no clinical benefit from influenza vaccination. Since influenza vaccination has been shown to be associated with pulmonary abnormalities after immunization in these patients, they should not be recommended for routine immunization against influenza. Among this particular group, control measures other than influenza vaccination, such as self-management programs aiming at reducing exacerbations of asthma or COPD, might be more effective. Collaborative efforts to introduce a stepped prevention program to improve influenza immunization practice in Dutch primary care have reached the main goal of high coverage. This succes was at least partly due to multi-faceted approach, the use of facilitating preventive software modules, and involvement of practice assistants.

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Summary

Influenza is responsible for considerable winter morbidity and mortality in temperate climates. Since the changes in antigenic make-up of the virus are unpredictable, the influenza virus will continue to exact its toll of morbidity and mortality unless preventive and therapeutic measures targeted at those who need them are implemented. As preventive health care budgets are limited, large-scale measures to control influenza should focus on individuals with a high probability of developing influenza-associated complications. Reported risk factors for serious influenza complications include age (notably infants and young children and the elderly), underlying disease, pregnancy and stay at nursing home or hospital. However, it is relatively unknown what role these risk factors play in different age subgroups or in primary care. Also, the statistical analysis of the available prognostic studies were not extended by developing a clinical prediction rule to estimate the probability of an individual developing complications enabling the identification of very high-risk persons.

The main option for reducing the impact of influenza is immunoprophylaxis with conventional inactivated vaccine. In influenza vaccine efficacy trials, most vaccinated children and young adults developed protective antibody titers against influenza with strains similar to vaccine components. Some studies suggest that elderly persons and patients with certain chronic diseases may develop lower titers. Large clinical effectiveness studies among the elderly established considerable reductions in serious end points due to the vaccine. To our knowledge, effectiveness studies among subgroups of elderly with high-risk medical conditions, high-risk children and patients of working-age are, however, lacking. Such studies are urgently needed to support evidence-based vaccination measures.

Finally, to be able to effectively control the public health burden associated with influenza, knowledge on the barriers to implement an effective immunization program is essential. Elements that should be targeted in a nationwide preventive program aiming at improving influenza vaccination practice in primary care and the effects of such a program need to be studied.

The three parts of this thesis therefore aim at filling some essential gaps in the scientific knowledge on (I) prognosis of influenza, (II) vaccine effectiveness in high-risk subgroups and (III) effects of implementing a nationwide primary care based influenza immunization program.

Part I Prognosis of influenza

In chapter 2 we determined prognostic factors for influenza-associated hospitalization or death among the adult vaccine target population with high-risk medical conditions during the 1996/97 influenza A epidemic. In a case-control study, the cases were either hospitalized or died due to influenza, bronchitis, pneumonia, diabetes, heart failure or myocardial infarction. GPs reviewed patient records of these cases and age- and sex-matched controls. It appeared that presence of chronic obstructive pulmonary disease, heart failure, previous hospitalization, high GP visiting rate and polypharmacy were important prognostic factors, particularly in patients of working-age.

In chapter 3 we developed a clinical prediction rule estimating the risk of hospitalization for influenza or pneumonia, or death using data from a database including 16,280 non-institutionalized and unvaccinated US senior citizens. Validation of the rule was conducted in various large cohorts of elderly members of three managed care organizations. The following predictors were selected by use of logistic regression analysis: age, sex, presence of pulmonary, cardiac and renal disease, dementia or stroke and cancer, number of outpatient visits and hospitalization for pneumonia and influenza in the previous year. The prognostic accuracy of the prediction rule in the derivation cohort was high when a cut-off sum-score ≥50 points is chosen (subjects with end point vaccinated: 89 percent, without end point unvaccinated: 51 percent) while only 50 percent of seniors would have to be selected for vaccination. The prediction rule might be of use to target preventive measures at those most likely to benefit.

Part II Clinical effectiveness of influenza vaccination

In chapter 4 we described several design and analytical methods aimed at limiting or preventing 'confounding by indication' in non-experimental safety and effectiveness studies. In short, comparison of study groups with similar prognosis, restriction of the study population and statistical adjustment for dissimilarities in prognosis are important tools. Various methods are illustrated using data of the prospective cohort study described in chapter 6.

In chapter 5 we described a two-season retrospective cohort study covering the 1995/96 and 1996/97 influenza A outbreaks in primary care. We included 349 patients with asthma aged between 0 and 12 years. The incidence of acute respiratory disease in unvaccinated children during the epidemics was 26 percent on average. In preschool children this incidence was highest (43 percent). The overall pooled clinical vaccine effectiveness was 27 percent (95

percent confidence interval -7 to 51 percent, p=0.11) after adjustments. A statistically higher pooled vaccine protectiveness of 55 percent (20 to 75 percent, p=0.01) was observed among preschool children with asthma compared with those between 6 and 12 years of age: -5 percent (–81 to 39 percent, p=0.85). We concluded that the incidence of acute respiratory disease among asthmatic children during influenza epidemics is very high, notably in the youngest. Influenza vaccination appears to reduce this morbidity in infants and preschool children with asthma.

In chapter 6 we assessed the clinical effectiveness and economical benefit of the influenza vaccination program in a general practice-based cohort of adult patients with chronic lung disease followed up during the 1995/96 influenza A epidemic. Computerized medical records of 1696 patients with chronic lung disease aged over 18 years were reviewed. The incidence of any complication, including low respiratory tract infection, acute cardiac disease or all cause death was 15 percent. Death, pneumonia, and acute cardiac disease were mainly limited to elderly patients. No effectiveness of the immunization program could be established in patients of working-age after adjustments for confounding. Among elderly vaccinees, the occurrence of any complication was reduced by 50 percent (95 percent confidence interval 17 to 70 percent). The economical benefit was estimated at £50 per elderly vaccinee. Immunization of elderly patients with chronic lung disease against influenza is effective and cost-saving. We further conclude that studies are needed to establish whether patients with pulmonary disease of working-age also benefit from vaccination.

We therefore conducted a prospective nested case-control study in 41 (1998/99 influenza B epidemic) and 52 (1999/2000 influenza A epidemic) primary care centers (chapter 7). We studied 4241 patients with asthma or COPD of working-age in season one and 5966 in season two. Patients developing fatal or non-fatal exacerbations of lung disease, pneumonia, heart failure, or myocardial infarction during either epidemic were considered cases. For each case, four age- and sex-matched controls were randomly sampled and patient records were reviewed. Severe morbidity, mainly respiratory, occurred in 13/1000 in season one and 34/1000 in season two. After adjustments, vaccination was not associated with reductions in complications (season one: odds ratio 0.94; 95 percent confidence interval, 0.26 to 3.48, season two: odds ratio 1.09; 95 percent confidence interval, 0.60 to 1.97, pooled odds ratio: 1.07; 95 percent confidence interval, 0.63 to 1.80). In a sample of 22 cases, 10 (46 percent) in season one and 11 of 20 cases (55 percent) in season two had influenza infection according to PCR analysis and only one control was positive for influenza. We concluded that influenza-associated respiratory morbidity in epidemics

frequently occurs among patients of working-age with asthma or COPD and that conventional influenza vaccination does not appear to reduce the incidence of this morbidity.

In chapter 8 we assessed the risk for hospitalization or death and the effectiveness of influenza vaccination among subgroups of elderly persons. In all, we included 122 974 and 158 454 elderly persons in the two study cohorts during the 1996/97 and 1997/98 influenza A seasons. Among unvaccinated persons, hospitalizations for pneumonia and influenza, or death occurred in 8/1000 healthy persons and 38/1000 high-risk persons in season one and 8/1000 and 29/1000 in season two. After adjustments, vaccination was associated with a 48 percent reduction in the combined outcome of hospitalization or death (95 percent confidence interval 40 to 52 percent) in season one and 31 percent (95 percent confidence interval 26 to 37 percent) in season two. Between 55 and 118 high-risk persons and between 264 and 290 healthy persons needed to be vaccinated to prevent one hospitalization or death. It appeared that influenza can cause significant morbidity and mortality in all subgroups of elderly persons. Also, individuals in both high-risk and healthy subgroups may substantially benefit from vaccination. However, the impact of influenza is highest in those with high-risk medical conditions.

Part III Implementation of influenza vaccination

In chapter 9 we reported organizational factors associated with a high influenza vaccination rate in a random sample of general practices, before large-scale implementation of a prevention program was fostered. Among 1251 practices, a high vaccination rate was associated with the use of personal reminders, monitoring patient compliance, marking risk patients in computerized patient records, a small number of patients per full-time practice assistant, urban areas, and single-handed practices. We concluded that improvement of vaccination rates in high-risk patients may be achievable by promoting the use of personal reminders and computerized patient records, as well as monitoring patient compliance and delegation of tasks to practice assistants.

In chapter 10 we reported the applicability of a computerized influenza prevention software module in four group practices of the Utrecht General Practitioners Network. By use of the module, 1104 previously unknown high-risk patients under 65 years were found. Application of the module increased the immunization rates over two years, specifically among those at highest risk for complications.

In chapter 11 we assessed the effectiveness of a nationwide multi-faceted prevention program involving general practitioners (GP) on influenza immunization practice using a before-and-after trial. During the period 1995-1997, a variety of methods was implemented to enhance the adoption of the immunization guideline by the physician, including employment of facilitators, small-group consensus meetings, individual instructions and introduction of supportive computer software. In 988 practices all influenza vaccination characteristics markedly improved from 1995 to 1997. Most significant changes were found in computerized marking and selection of high-risk patients, and sending personal reminders. Vaccine uptake significantly increased from 9 to 16 percent of the practice population. We concluded that a coordinated approach involving primary care physicians can succeed in enlarging the public health impact of a population-based preventive measure.

In chapter 12, the implications of our findings from the studies in this thesis are discussed and suggestions for future research are given.

In conclusion, prognostic information on influenza and its complications is essential to direct preventive measures at those who need it and such information should be incorporated into the recommendations for routine influenza immunization and planning of actions in case an influenza pandemic might occur. Our influenza vaccine effectiveness studies demonstrate health benefits among very young children with asthma, and among the elderly. Efforts should be renewed to target these vulnerable patient groups to be immunized against influenza. Among patients of working-age with asthma or COPD there was a lack of any benefit from influenza vaccination and this large group of patients should therefore not be recommended for routine vaccination. Collaborative efforts to introduce a step-wise prevention program with the aim to improve influenza immunization practice in primary care reached the main goal of a high influenza vaccination rate. Our studies demonstrate that the use of facilitating software modules and involvement of practice assistants are essential in successful implementation of preventive health care.

Samenvatting

Influenza is elk jaar verantwoordelijk voor aanzienlijke morbiditeit en mortaliteit in landen met een gematigd klimaat. Omdat de antigene samenstelling van nieuwe influenzavirussen onvoorspelbaar is, zal influenza de oorzaak van veel ziekte en sterfte blijven, tenzij preventieve of therapeutische maatregelen worden genomen voor degenen die hiervoor het meest in aanmerking komen. Daar de budgetten voor preventieve programma's beperkt zijn, is het noodzakelijk dat grootschalige maatregelen, om de effecten van influenza te minimaliseren, zich moeten richten op individuen met een gemiddeld hoog risico op complicaties van influenza. Beschreven risicofactoren voor ernstige complicaties zijn leeftijd (vooral babies en peuters, en ouderen), het hebben van een chronische risicoziekte, zwangerschap, en verblijf in een verpleeghuis of ziekenhuis. Het is alleen nog relatief onbekend welke rol de risicofactoren spelen in verschillende leeftijdsgroepen of in de eerste lijn. Bovendien beschrijven de beschikbare prognostische onderzoeken geen ontwikkeling van een klinische predictieregel waarmee de individuele kans op het krijgen van een complicatie voorspeld kan worden. Een dergelijke regel maakt het mogelijk om personen met een gemiddeld hoog risico te identificeren.

De belangrijkste mogelijkheid om de gevolgen van influenza tegen te gaan, is vaccineren met het conventionele influenzavaccin. Uit experimenteel onderzoek naar de werking van influenzavaccinatie is gebleken dat de meeste kinderen en volwassenen in de werkbare leeftijd een beschermende antistoftiter ontwikkelen tegen influenzavirussen met dezelfde antigene samenstelling als de componenten van het vaccin. Sommige onderzoeken hebben laten zien dat ouderen en patiënten met risicoziekten soms lagere antistoftiters ontwikkelen na vaccinatie. Echter, uit grootschalige onderzoeken onder ouderen bleek dat het aantal complicaties tijdens een influenza epidemie wel degelijk teruggebracht werd door vaccinatie. Zover we weten zijn er geen effectiviteits-onderzoeken naar influenzavaccinatie uitgevoerd bij subgroepen van oudere personen met verschillende risicofactoren, of bij kinderen of volwassenen in de werkbare leeftijd met een risicoziekte. Dit soort onderzoeken zijn noodzakelijk om het vaccinatiebeleid volledig te kunnen onderbouwen.

Om uiteindelijk de maatschappelijke gezondheidslast die veroorzaakt wordt door influenza te kunnen tegengaan, dient er tenslotte kennis gegenereerd te worden over de hindernissen die er zijn om een effectief vaccinatieprogramma te implementeren. Daartoe dienen de elementen van een nationaal programma in de eerste lijn, die aangepakt moeten worden tijdens de implementatie, verder te worden onderzocht.

De drie delen van deze thesis hebben daarom als doel een aantal essentiële gebreken in de bestaande wetenschappelijke kennis aan te vullen op het gebied van: (I) prognose van influenza, (II) effectiviteit van vaccinatie bij subgroepen, en (III) effecten van het implementeren van een nationaal eerstelijns influenzavaccinatie-programma.

Deel I Prognose van influenza

In hoofdstuk 2 hebben we prognostische factoren bepaald voor ziekenhuisopname of sterfte tijdens de 1996/97 influenza A epidemie bij een doelgroep van volwassen patiënten met chronische ziekten. In een patiënt-controle onderzoek werden de patiënten gedefinieerd als diegenen die volgens de richtlijnen voor influenzavaccinatie in aanmerking kwamen op grond van comorbiditeit en die opgenomen waren in het ziekenhuis tengevolge van influenza, bronchitis, pneumonie, diabetes, hartfalen, hartinfarct, of hieraan waren overleden tijdens de epidemie. De huisarts verstrekte over zowel de patiënten als de controles dezelfde medische informatie aan de hand van het elektronisch medisch dossier. Het bleek dat de aanwezigheid van COPD, hartfalen, voorafgaande hospitalisatie, hoge consultatiefrequentie en polyfarmacie onafhankelijke prognostische factoren waren, met name bij patiënten in de werkbare leeftijd.

In hoofdstuk 3 hebben we de ontwikkeling beschreven van een klinische predictieregel om het absolute risico op ziekenhuisopname voor influenza of pneumonie, of sterfte te schatten. Dit gebeurde met behulp van data van 16.280 Amerikaanse ouderen die niet waren opgenomen in een verpleeg- of bejaardenhuis en ongevaccineerd waren. Validering van de regel is uitgevoerd met behulp van verschillende grote cohorten gevaccineerde en ongevaccineerde ouderen die lid waren van drie Amerikaanse gezondheidszorgorganisaties. De volgende predictoren werden geselecteerd met behulp van logistische regressie-analyse: leeftijd, geslacht, aanwezigheid van pulmonaire, cardiale of nierziekte, dementie of hersenbloeding of kanker, het aantal consulten in de polikliniek van het ziekenhuis en voorafgaande ziekenhuisopname voor pneumonie of influenza. De predictieregel was accuraat in het derivatiecohort, indien een afkappunt somscore van 50 punten werd gehanteerd (het aantal personen met een eindpunt dat wordt gevaccineerd is 89%, zonder eindpunt wordt 51% gevaccineerd), terwijl slechts de helft van het totaal aantal ouderen wordt geselecteerd voor extra zorg.

Deel II Klinische effectiviteit van influenzavaccinatie

In hoofdstuk 4 beschrijven we verschillende onderzoeksontwerpen en analytische methoden om 'systematische vertekening door indicatiestelling' of 'confounding' in niet-experimentele veiligheids- en effectiviteitsonderzoeken te minimaliseren. In het kort zijn de belangrijke strategieën: de vergelijking van onderzoeksgroepen met vergelijkbare prognose, restrictie van de onderzoekspopulatie en statistische aanpassingen voor ongelijke verdeling van prognose tussen de groepen. De verschillende methoden om confounding tegen te gaan worden geïllustreerd aan de hand van data van het onderzoek uit hoofdstuk 6.

In hoofdstuk 5 beschrijven we een eerstelijns retrospectief cohort onderzoek onder 349 kinderen met astma in de leeftijd tot en met 12 jaar, die werden gevolgd gedurende twee influenza A seizoenen (1995/96 en 1996/97). De incidentie van acute respiratoire ziekte bij ongevaccineerde kinderen tijdens de influenza-epidemieën was gemiddeld 26 procent. Bij kinderen onder de 6 jaar was deze incidentie het hoogst: 43 procent. De gepoolde klinische effectiviteit van het influenzavaccin bleek 27% (95% betrouwbaarheidsinterval (b.i.) −7 tot 51%, p=0.11) na controle voor confounding in de regressie-analyse. Een statistisch significant groter effect van vaccinatie van 55% (95% b.i. 20 tot 75%, p=0.01) werd waargenomen bij de jongere kinderen tot 6 jaar. Bij de oudere kinderen was dit −5% (95% b.i. −81 tot 39%, p=0.85). We concluderen dat de incidentie van acute respiratoire morbiditeit hoog is bij kinderen met astma, met name bij de jongsten. Bij deze kinderen met astma jonger dan 6 jaar blijkt influenzavaccinatie de morbiditeit in belangrijke mate te reduceren.

In hoofdstuk 6 hebben we de klinische effectiviteit en de economische voordelen van het influenzavaccinatie programma bestudeerd bij volwassen patiënten met chronische longziekten. Het onderzoek betrof de 1995/96 influenza A epidemie. Informatie werd verstrekt aan de hand van de elektronische medische dossiers van 1696 patiënten van 18 jaar en ouder. De incidentie van complicaties zoals lage luchtweginfectie en pneumonie, acute hartziekte of sterfte was 15 procent. Sterfte, pneumonie en hartziekte kwamen voornamelijk voor bij de oudere patiënten van 65 jaar en ouder. Bij patiënten tussen de 18 en 64 jaar vonden we geen aanwijzingen dat influenzavaccinatie het optreden van de complicaties verminderde. Daarentegen bleek de reductie in het optreden van complicaties door vaccinatie bij ouderen 50% (95% b.i. 17 tot 70%). We schatten dat er bij oudere longpatiënten ongeveer fl.175,- per gevaccineerde wordt bespaard. Verder concludeerden we dat er meer onderzoek nodig is naar de effectiviteit van influenzavaccinatie bij volwassen longpatiënten onder de 65 jaar.

Daarom werd een prospectief genesteld patiënt-controle onderzoek uitgevoerd in 41 (1998/99 influenza B epidemie) en 52 (1999/2000 influenza A epidemie) huisartspraktijken (hoofdstuk 7). We bestudeerden 4241 patiënten met COPD en astma in de werkbare leeftijd in seizoen 1 en 5966 patiënten in seizoen 2. In het patiënt-controle onderzoek werden de patiënten gedefinieerd als personen uit het baseline cohort die een diagnose hadden van een fatale of niet-fatale exacerbatie van het onderliggend longlijden, pneumonie, hartfalen of hartinfarct gedurende de epidemie. Voor elke patiënt werden er aselect 4 leeftijds- en geslacht gematchte controles getrokken die op dat moment geen complicatie hadden. Van alle onderzoekspersonen werd klinische informatie middels het medisch dossier verzameld. Ernstige morbiditeit, met name respiratoir, vond plaats bij 13 van de 1000 personen in seizoen 1 en 34 van de 1000 personen in seizoen 2. Na controle voor vertekening door indicatiestelling, bleek vaccinatie niet geassocieerd met reducties in complicaties (seizoen 1: odds ratio 0.94; 95% b.i. 0.26-1.97, seizoen 2: odds ratio 1.09; 95% b.i. 0.60-1.97; gepoolde data: odds ratio 1.07; 95% b.i. 0.63-1.80). Van de 22 patiënten waarbij in het eerste seizoen een neus-keelwat werd afgenomen, bleken 10 (46%) een positieve PCR voor influenza te hebben en 11 van de 20 (55%) patiënten in seizoen 2 hadden influenza. Slechts één controle was positief voor influenza (seizoen 2). We concludeerden dat respiratoire morbiditeit tijdens influenza-epidemieën frequent voorkomt bij patiënten met astma of COPD in de werkbare leeftijd, maar dat de conventionele influenzavaccinatie deze morbiditeit niet voorkomt.

In hoofdstuk 8 hebben we bij subgroepen van ouderen de kans op ziekenhuisopname tengevolge van influenza of pneumonie, of overlijden bepaald en de effectiviteit van het influenzavaccin. Totaal werden 122.974 en 158.454 ouderen in de twee cohorten gedurende de 1996/97 en 1997/98 influenza A seizoenen gevolgd. Bij de gezonde ongevaccineerde ouderen kwam ziekenhuisopname of sterfte bij 8 van de 1000 personen voor en bij de ouderen met risico-aandoeningen bij 38 van de 1000 personen in het eerste seizoen. Deze getallen waren 8 van de 1000 en 29 van de 1000 personen respectievelijk, in het tweede seizoen. Na controle voor confounding, bleek influenzavaccinatie geassocieerd met een 48 procent reductie in de gecombineerde uitkomstmaat (95% b.i. 40 tot 52%) in het eerste seizoen en met 31% (95% b.i. 26 tot 37%) in het tweede seizoen. Tussen de 55 en 118 ouderen met risico-aandoeningen en tussen de 264 en 290 gezonde personen moesten worden gevaccineerd om één ziekenhuisopname of overlijden te voorkomen. Geconcludeerd kan worden dat influenza een belangrijke oorzaak is van ziekte of sterfte bij alle subgroepen ouderen. Daarnaast blijken zowel oudere risicopatiënten als gezonde ouderen baat te hebben bij vaccinatie. Echter, de

invloed van influenza en daarmee vaccinatie is het grootst bij ouderen met co-morbiditeit.

Part III Implementatie van influenzavaccinatie
In hoofdstuk 9 rapporteerden we de organisatiefactoren die samenhingen met een hoge influenzavaccinatie graad in een aselecte steekproef van Nederlandse huisartspraktijken voordat een grootschalig preventieprogramma werd geïnitieerd. Uit de analyse van gegevens van 1251 praktijken bleek dat een hoge vaccinatiegraad samenhing met het gebruik van een persoonlijke oproep door de huisarts, het monitoren van de opkomst, het markeren van patiënten in een geautomatiseerd medisch dossier, een klein aantal patiënten per fulltime praktijkassistente, en stedelijke gebieden en solopraktijken. We concludeerden dat verbetering van de vaccinatiegraad bij risicopatiënten haalbaar is indien het persoonlijke oproepen door de huisartsen en de monitoring van de opkomst wordt gestimuleerd als ook indien een groot deel van de vaccinatietaken wordt gedelegeerd aan de praktijkassistente.

In hoofdstuk 10 beschreven we de toepasbaarheid van de 'griepmodule' software in vier groepspraktijken van het Huisartsen Netwerk Utrecht. Door het gebruik van de module werden 1104 risicopatiënten onder de 65 jaar opgespoord die eerder niet bekend waren bij de huisarts. Door het gebruik van de griepmodule gedurende twee opvolgende jaren nam de vaccinatiegraad toe, met name bij degenen die het hoogste risico lopen op complicaties.

In hoofdstuk 11 bepaalden we de effecten van een nationaal eerstelijns preventieprogramma waarin verschillende voorlichtingskundige methodieken werden gehanteerd. De effecten op de influenzavaccinatie praktijk werden beschouwd met behulp van een voor-en-na vergelijking. Gedurende de periode 1995-1997 werden begeleiders in het veld aangesteld, kleine groepsbijeenkomsten en individuele instructies georganiseerd en de 'griepmodule' ontwikkeld om de huisarts volgens de NHG Standaard 'Influenza en influenzavaccinatie' te laten werken. Uit gegevens van 988 huisartspraktijken bleek dat alle vaccinatiekarakteristieken behoorlijk verbeterden tussen 1995 en 1997. De meest in het oogspringende verbeteringen werden geconstateerd bij het geautomatiseerd markeren en selecteren van risicopatiënten en het sturen van persoonlijke oproepen. De vaccinatiegraad van de praktijkpopulatie steeg van 9 naar 16 procent. We concludeerden dat een gecoördineerde benadering, waarin huisartsen worden betrokken, er in kan slagen om de invloed van een populatiegerichte preventieve maatregel op de gezondheidszorg te vergroten.

In hoofdstuk 12 zijn de implicaties van onze bevindingen uit de onderzoeken van deze thesis bediscussieerd en er zijn suggesties gegeven voor vervolgonderzoek.

Concluderend kan gesteld worden dat prognostische informatie over influenza en complicaties essentieel is om preventieve maatregelen te richten op degenen die daarvoor het meest in aanmerking komen. Dergelijke informatie zou moeten worden opgenomen in de aanbevelingen voor influenzavaccinatie en in de planning van maatregelen ten tijde van een influenza pandemie. Onze onderzoeken naar de effectiviteit van influenzavaccinatie hebben laten zien dat influenzavaccinatie gezondheidsvoordelen oplevert voor zeer jonge kinderen met astma en alle ouderen. We zouden opnieuw inspanningen moeten verrichten om deze groepen te immuniseren tegen influenza. Bij patiënten met astma en COPD tussen de 18 en 64 jaar konden we geen effecten van vaccinatie vaststellen en deze grote groep van patiënten zou daarom niet meer in aanmerking moeten komen voor routinematige vaccinatie. Het door inspanning van vele organisaties geïntroduceerde stapsgewijze preventieprogramma 'Preventie: maatwerk', met als doel de influenzavaccinatie graad onder risicopatiënten te verhogen in de eerste lijn, bereikte dit doel. Onze onderzoeken lieten zien dat het gebruik van ondersteunende software modules en het inzetten van de praktijkassistente essentieel zijn voor een succesvolle implementatie van preventieve huisartsgeneeskundige zorg.

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Dankwoord

Hoewel de formele contacten met collega's reeds gewaardeerd zijn door middel van auteurschap of vernoeming in de 'Acknowledgements', wordt het plezier in het werk grotendeels bepaald door de informele contacten waarvoor mijns inziens aandacht behoort te zijn in ieder proefschrift.

Prof. dr. R.A. de Melker, beste Ruut: als voormalig hoofd van de vakgroep Huisartsgeneeskunde Utrecht, heden Julius Centrum voor Huisarts-geneeskunde en Patiëntgebonden Onderzoek, stond jij aan de basis van dit werk. Het belang dat jij hecht aan epidemiologen heb ik door geen ander zo vaak zien verwoorden. Ik waardeerde je betrokkenheid bij zowel je personeel als de huisartsen waarvoor dit tenslotte allemaal is bedoeld.

Mijn eerste promotor, prof. dr. A.W. Hoes, beste Arno: als opvolger van prof. dr. F.W.M.M. Touw, bracht je de epidemiologie op de vakgroep op een hoger plan. Het door mij als stimulerend ervaren leraar-leerling gevoel werd vooral aangewakkerd door je kritische houding ten aanzien van methodologie en kretologie. Je know-how op het gebied van patiënt-controle onderzoek en huisartsgeneeskundig onderzoek is essentieel gebleken voor een groot deel van dit proefschrift.

Mijn tweede promotor, prof. dr. Th.J.M. Verheij, beste Theo: jij volgde prof. dr. R.A. de Melker op als nieuw hoofd van de vakgroep en bent coördinator van de onderzoekslijn Infectieziekten. Je kennis op het gebied van de diagnostiek en behandeling van lage luchtweginfecties was van belang voor de interpretatie van menig (on)verwacht onderzoeksresultaat. Je betrokkenheid bij de projecten was groot en je wist steeds opnieuw aandacht te vragen voor het huisartsenperspectief.

Mijn opleider Klinische Epidemiologie, prof. dr. D.E. Grobbee, beste Rick: hoewel jij aan de zijlijn hebt gestaan bij de projecten uit dit proefschrift, heb je er mede voor gezorgd dat ik post-academisch onderwijs op de prestigieuze Johns Hopkins University in Baltimore kon volgen en stimuleerde je het opdoen van internationale ervaring in Minneapolis. Arno en jij hebben verder op zorgvuldige en ervaren wijze zorggedragen voor de finesses in het onderzoek en rapportage.

Prof. dr. K.L. Nichol, dear Kristin: I am honoured that you invited me to collaborate in your influenza monitoring and evaluation programme covering three US health plans. For epidemiologists, the size of the cohorts you were

able to follow from 1996 on is nothing but a dream. I wish to thank you for the experienced and efficient way you supervised the two projects of chapter 3 and 8. I hope this work is a foundation for future collaboration. I am looking forward to seeing you and the other friendly colleagues of the VA Medical Hospital again when working with you on other projects.

Ook de stafleden van de afdeling Huisartsgeneeskunde van het Julius Centrum verdienen een woord van dank. Dr. W.A.B. Stalman, beste Wim: jij was coördinator van het Huisartsen Netwerk Utrecht (HNU) en begeleider bij een aantal projecten waaronder het KEA project bij kinderen met astma (hoofdstuk 5) en het griepmodule-onderzoek (hoofdstuk 12). Je enthousiasme en motiverende bijdrage gedurende al die jaren dat het netwerk moest worden opgebouwd om de deelnemende huisartsen onderzoeks-minded te maken en te houden was groot. Ik denk dat ik namens het hele HNU spreek als ik zeg dat het een gemis is voor ons dat jij nu een huisartsennetwerk zal gaan opbouwen als hoogleraar aan de VU in Amsterdam.
Dr. G.A. van Essen, beste Ted: samen met Dr. M.M. Kuijvenhoven heb jij mij begeleid bij de evaluatie van het inmiddels beroemde en soms verguisde 'Preventie: maatwerk' project. Jij leerde mij de fijne kneepjes van het vak. Je kennis op het gebied van beleid bij influenza en preventie kon ik goed gebruiken om de epidemiologische onderzoeken in perspectief te plaatsen.
Dr. M.M. Kuijvenhoven, beste Marijke: jij hebt aan de basis gestaan van de onderzoeken op het gebied van compliance bij influenzavaccinatie en het bovengenoemde evaluatie-onderzoek. Als gedragswetenschapper bracht je de expertise in die nodig was om deze voorlichtingskundige projecten vorm te geven. Hoewel je momenteel meer bij onderwijs betrokken bent, draag je op toegewijde wijze zorg voor de voortzetting van belangrijk voorlichtingskundig en implementatie onderzoek binnen de infectieziektenlijn.
Dr. A.O. Quartero en Dr. R.A.M. Damoiseaux, beste Otto en Roger: we begonnen tegelijkertijd ons promotie-onderzoek. De 'SOEP-besprekingen' evenals jullie humor heb ik zeer gewaardeerd. De andere onderzoeksstafleden, Mattijs, Niek, Marie-Louise, Frank en Alfred: jullie hebben slechts weinig meegekregen van de cyclische manie die iedere winter weer toesloeg bij de 'influenza-onderzoekers'. Dank voor het commentaar op rapportages en voorstellen.

De onderzoeken waren niet tot stand gekomen zonder ondersteuning. Ir. F.A. Leffers, beste Fred: niet alleen was jij de stille motor achter het 'SPICA' project (hoofdstuk 7), je was bovenal voor lange tijd mijn buurman. We hebben veel samen gedeeld en ik mis nog steeds de lachsalvo's waardoor we vaak boze blikken ontlokten bij de buren. Hoewel bijna niemand begreep wat jij nou

eigenlijk deed, kan ik zeggen dat slechts weinig mensen zoveel abstractievermogen en technisch inzicht hebben als jij. Je capaciteiten zijn daarmee mijns inziens onderschat geweest en het is een persoonlijk maar ook collegiaal gemis dat je naar het Trimbos Instituut bent gegaan.
Carla Tims, jij was als hoofd datamanagement van het opgeheven IC verantwoordelijk voor een belangrijk deel van de dataverzameling. Je hebt me hierover veel geleerd. Meer nog dan dat was je in staat het IC tot familiebedrijf te maken. Ook de andere ex-leden van het IC familiebedrijf: Inge (op jou kom ik later nog terug), Bep, Aart en Bert, jullie zorgden ervoor dat ik me snel thuis voelde en onze gezellige IC-etentjes zal ik niet snel vergeten. Aart, evenals bij andere promovendi, heb je mij destijds geweldig geholpen met statistische analyses waarvan ik het bestaan niet eens wist. Op vakkundige wijze nam Peter Zuithoff die taak over.
Het secretariaat was essentieel bij de ondersteuning van de projecten: Marian en Diana, jullie hebben mij vanaf het begin geholpen om de administratie en monitoring van 'Preventie:maatwerk' rond te krijgen. Later hebben jullie als onderzoeksassistenten een belangrijke rol gespeeld in het SPICA-team. Er is de laatste jaren veel veranderd, maar ik hoop dat jullie in de toekomst nog met veel plezier de puntjes op de I zullen zetten.
Anderen die een bijdrage leverden aan dit proefschrift waren: Bram Smits, Titia Spijkerman en Bert Visbeek, allen basisarts. Bram: jij trok ongekend enthousiast de kar bij het astmakinderen project (hoofdstuk 5). Titia en Bert: dank voor jullie inzet bij de griepmodule-onderzoeken van het eerste uur.

En dan de hele en halve promovendi: Catherine Weijnen, Sandra van Loon, Ineke Welschen, Frans Rutten, Birgit van Staaij, Rene Bijkerk, Wim Opstelten, Lex Goudswaard, Ruud Oudega, Henriette Hendriks, en Cees van Beek, dank voor alle gespreksstof tijdens de lunches. Catherine: jij neemt als nieuwe kamergenoot een aparte plaats in. Het is wonderlijk dat we nog zoveel onderzoek doen naast onze vele conversaties. Jij bent in mijn ogen de huisarts-onderzoeker van de toekomst: altijd kritisch en patiëntgericht. Sandra: jij zult het stokje van me overnemen als onderzoeker op het project PRISMA (PRevention of Influenza, Surveillance and Management) en ik heb er alle vertrouwen in dat je dit grootschalige project tot een goed einde zult brengen. Wim en Frans: hoe zat het nou ook weer met die polytome logistische regressie?

Voor de goede sfeer op de afdeling zijn ook vele anderen verantwoordelijk. Ineke van den Hoeven: jij neemt niet alleen als receptioniste een belangrijke plaats in. Voor alle praktische problemen waarvoor ik niet bij een ander terecht kan, kan ik altijd bij jou terecht. Hans Eeckhout: altijd in voor een geintje.

Bert-jan: nu ook onderzoeker, wel een beetje een stijve. En alle anderen van de 'andere kant': bedankt voor de 'koffietijd'.

Sinds kort heten we Julius Centrum, een samenvoeging van Public Health, MTA, Epidemiologie en Huisartsgeneeskunde. Dr. E. Buskens, beste Erik: jij bent samen met Yolanda en Ale degene van de epidemiologische D-vleugel die mij nog kent van de MAS-periode. Bedankt dat ik gebruik heb kunnen maken van je kennis op het gebied van de kosten-effectiviteitsberekeningen.

Binnen het UMCU heb ik samen mogen werken met enkele klinisch specialisten: Prof. dr. J.W.J. Lammers, beste Jan-Willem: jouw klinische expertise op het gebied van de lage luchtweginfecties bij astma en COPD was onontbeerlijk voor het SPICA-project. Dr. A.M. van Loon, beste Ton: het gehele virologische deel van het SPICA-project werd onder jouw verantwoording op efficiënte wijze uitgevoerd. Prof. dr. I.M. Hoepelman, beste Andy: hoewel je niet direct bij dit proefschrift betrokken was, heb je een essentiële bijdrage geleverd aan mijn artikelen en voorstellen betreffende de pneumokokkenvaccinatie.

Ook wil ik enkele collega's werkzaam op andere locaties bedanken. Rosella Hermens, werkzaam op het WOK in Nijmegen: ik heb plezierige herinneringen aan onze samenwerking tijdens het 'Preventie:maatwerk' project. Je hebt mij geweldig geholpen met de evaluatie op het gebied van de influenzavaccinatie en ik heb met genoegen mee mogen denken met jouw artikelen op het gebied van de cervix-screening. Hoogtepunten waren vooral het WONCA congres in Praag en de 'verzenddagen' waarbij op het ritme van housemuziek vele duizenden vragenlijsten werden ingepakt. Rianne Lafeber, momenteel epidemioloog op het RIVM: jij hebt destijds op fanatieke wijze het onderzoek gestart, beschreven in hoofdstuk 2. 'IBB' hoor ik gelukkig nog regelmatig.

Huisartsgeneeskundig onderzoek valt of staat met de participatie van huisartsen. Ik ben dankbaar dat ondanks de grote praktijkbelasting velen bereid waren tijd en energie te steken in onderzoek waarvan je van tevoren nooit weet waartoe het leidt. Met name wil ik hier noemen de contactpersonen van het HNU: Ron Pieters, Ria van den Broek, Mieke van Dillen, Gerard Daggelders, IJsbrand Stoutenbeek en Eric Hendrickx. De vele vergaderingen die ik met jullie en Wim heb mogen meemaken waren altijd gezellig en opbouwend. Jullie kritische commentaar heeft mij vaak behoed voor praktische problemen. IJsbrand: jij neemt een aparte plaats in omdat je korte tijd werkzaam bent geweest voor het HNU. Jouw humor was geweldig. Ook de vele huisartsen die

eerst aan het 'Preventie:maatwerk' onderzoek meewerkten, daarna aan SPICA en momenteel aan PRISMA ben ik zeer veel dank verschuldigd voor de enthousiaste inzet.

Velen hebben gezorgd dat er ook een fantastisch leven naast het werk is, alhoewel soms in verhouding te kort. Pieter: onze 'wereldreis' door Nieuw-Zeeland en Australië was onvergetelijk. Ed: we hebben de Noordkaap bereikt! Leden van het Maarssens Fanfare Corps: muziek is ontspanning! Ik kan het als lid van de PR-commissie niet laten reclame te maken. Rob en Atie van Doornik: jullie zijn fantastische ouders. Rob: binnen 5 minuten was het cover-design bedacht, eenvoudig en strak. Tako en Paulien, Robin en Kyara: het is een genot jullie als gezin te zien groeien. Tako: jij laat zien dat creatieve vrije ondernemers veel kunnen bereiken. Paps: ik vergeet nooit je niet aflatende enthousiasme toen je mij meesleepte naar alle universitaire opleidingen die enigszins met gezondheid te maken hadden. Mams: jouw bijvoeding tijdens het leren voor de tentamens heeft mij de opleiding Gezondheidswetenschappen als basis voor deze thesis succesvol doen afronden. De beide paranymfen Sylvia van Woudenberg en Vincent van Doornik wil ik bedanken voor de broodnodige ondersteuning tijdens de voorbereidingen van dit grote gebeuren.

Inge: jij bent het belangrijkst voor mij. Ik leer veel van je en ik ben gelukkig met de manier waarop we ons leven inrichten. Samen dromen is van levensbelang en dat zullen we ook hierna blijven doen.

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Curriculum vitae

Eelko Hak was born on December 7th, 1968 in Vlaardingen, the Netherlands. He attended secondary school (Atheneum B) at the Dr. F.H. de Bruijne Lyceum in Utrecht. In 1987, he started his academic studies Health Sciences at the Faculty of Medicine, Catholic University of Nijmegen. During his studies, he specialized in epidemiology and followed academic courses on health education at the Agricultural University Wageningen as well. His first elective was spent in Ebolowa, Cameroon, in which he participated in a trial on the effectiveness of prophylactic use of anti-malarials in pregnant women (Head: dr. M. Cot). He finalized his studies in 1993 with an elective focusing on prognostic factors for diarrhea and malaria among travelers at the Municipal Health Center of Amsterdam (Head: dr. A. Leentvaar-Kuijpers) and became certified after his graduation as MSC in Epidemiology. Before serving the military service as a musician, he conducted a quasi-experiment as part of the KNOOP-project at the Department of Epidemiology, Catholic University of Nijmegen (Head: Prof. dr. G.A. Zielhuis). In 1994, he was appointed epidemiologist at the Department of Clinical Epidemiology, Academic Hospital Utrecht (Head: Prof. dr. Y. van der Graaf) and analyzed and reported data of the Multi-center Aneurysm Study. He continued his career in 1995 at the Department of General Practice, Faculty of Medicine, University Utrecht, since 1997 renamed Julius Center for General Practice and Patient Oriented Research, University Medical Center Utrecht (Head and supervisor: Prof. dr. D.E. Grobbee). As part of his appointment, he started the studies described in the third part of his thesis on implementation of influenza vaccination (former head: Prof. dr. R.A. de Melker). In 1998, he received funding from the Asthma Foundation for his proposal to conduct the study described in Chapter 7 (Heads: Prof. dr. A.W. Hoes and Prof. dr. Th.J.M. Verheij). Since 1995, he received training in epidemiological research at the New England Epidemiological Summer School in Boston (1996) and followed postgraduate courses (NIHES) in the Netherlands. He further specialized in infectious disease epidemiology during a summer course at the Johns Hopkins University in Baltimore. In 1999, he won a travel award for PHD students of the Graduate School Infection and Immunity. He also received the ONVZ Prevention 2000 Prize for his article described in chapter 6. During the summer of 2000 he conducted the studies described in Chapter 3 and 8 at the VA Medical Center, Minneapolis, USA (Head: Prof. dr. K.L. Nichol). Since October 2000, he is appointed assistant professor of infectious disease epidemiology at the Julius Center and Department of Internal Medicine, University Medical Center Utrecht. He is married to Inge van Doornik, coordinator health centers, Stichting Gezondheidscentra Leidsche Rijn, Utrecht.