Clinical Effectiveness of Influenza Vaccination in Persons Younger Than 65 Years With High-Risk Medical Conditions

The PRISMA Study

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Background: Influenza vaccination has consistently been shown to prevent all-cause death and hospitalizations during influenza epidemics among seniors. However, such benefits have not yet been demonstrated among younger individuals with high-risk medical conditions. In the present study, we evaluated the effectiveness of influenza vaccine in persons recommended for vaccination of any age during an epidemic.

Methods: We conducted a case-control study during the 1999-2000 influenza A epidemic nested in a cohort of 75 227 primary care patients. End points were all-cause mortality and episodes of hospitalizations or general practitioner (GP) visits for influenza, pneumonia, other acute respiratory disease, acute otitis media, myocardial infarction, heart failure, and stroke. The effectiveness of vaccination was evaluated by means of logistic regression analysis with adjustments for age, sex, prior health care use, medication use, and comorbid conditions.

Results: Among high-risk children and adolescents younger than 18 years (n=5933; 8% of the study population), 1 death, 3 hospitalizations for pneumonia, and 160 GP visits occurred. After adjustments, 43% (95% confidence interval [CI], 10%-64%) of visits were prevented. Among high-risk adults aged between 18 and 64 years (n=24 928; 33% of the study population), 47 deaths, 23 hospitalizations, and 363 GP visits occurred. After adjustments, vaccination prevented 78% of deaths (95% CI, 39%-92%), 87% of hospitalizations (95% CI, 39%-97%), and 26% of GP visits (95% CI, 7%-47%). Among elderly persons (n=44 366; 59% of the study population), 272 deaths and 166 hospitalizations occurred, and after adjustments the vaccine prevented these end points by 50% (95% CI, 23%-68%) and 48% (95% CI, 7%-71%), respectively.

Conclusion: Persons with high-risk medical conditions of any age can substantially benefit from annual influenza vaccination during an epidemic.

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INFLUENZA CONTINUES TO BE A MAJOR cause of annual morbidity and mortality.[1,2] Serious complications include pneumonia,[2,3] acute otitis media[4] and exacerbations of acute pulmonary,[5] cardiac, or cerebrovascular disease.[2,6,7] In the United States each year, 140 000 hospital admissions and over 36 000 deaths are attributed to influenza.[8] Corresponding figures of excess deaths reported for European countries such as the United Kingdom, Denmark, and the Netherlands are 11 000,[9] 400,[10] and 2000, respectively.[11]

Many studies have shown that influenza vaccination can reduce the occurrence of hospitalizations for acute respiratory disease and all-cause death among the elderly.[12-15] Recently, Nichol and colleagues[7] also demonstrated considerable reductions in acute cardiovascular disease and stroke during epidemics in the same group. Moreover, economic evaluations indicate cost savings across different countries.[16] Therefore, seniors are strongly recommended for vaccination and vaccination rates have been on the rise.[17] Immunization guidelines, however, also include younger persons at risk because of high-risk conditions such as chronic lung and heart disease, but vaccination rates are lagging far behind the health objectives of many countries. At present, more than 20% of the Dutch population is targeted for annual vaccination, 40% of whom are younger than 65 years.[17] For the United States it has been estimated that about 50% of the target population is younger than 65 years (24 million working-age adolescents and 8 million high-

risk children) and vaccination rates are below 40%.[1] The low vaccine coverage in these younger groups might in part be explained by the lack of evidence supporting the clinical effectiveness of vaccination.

To gain more insight into the impact of influenza and possible health and economical benefits of vaccination across age groups, we set up the primary care–based Prevention of Influenza, Surveillance, and Management (PRISMA) study.[18] As part of this study, we used a case-control approach nested in a large cohort of persons recommended for vaccination to estimate the effectiveness of influenza vaccination in reducing serious complications during the 1999-2000 influenza A epidemic among high-risk children and adolescents younger than 18 years, high-risk adults aged between 18 and 64 years, and elderly persons 65 years or older.

METHODS

SOURCE POPULATION

The design of the PRISMA study has been described elsewhere.[18] Briefly, we conducted the study during the 1999-2000 influenza A epidemic and 2 consecutive seasons in which the influenza activity was virtually absent (2000-2001 season) or mild (2001-2002 season; **Figure**). For the present study, we therefore choose to analyze the data of cases and controls ascertained during the 1999-2000 influenza A epidemic in the period from week 50 in 1999 to week 10 in 2000. We identified a cohort of patients eligible for annual influenza vaccination according to Dutch primary care immunization guidelines prior to the study season. The Dutch guideline recommends influenza vaccination for persons 65 years or older and younger persons with a high-risk medical condition including chronic bronchitis, emphysema, asthma, other respiratory diseases, acute or chronic ischemic heart disease, heart failure, atrial fibrillation, other heart disease, cerebrovascular disease, diabetes mellitus, chronic renal disease, chronic staphylococcal infection, and immune-related diseases and patients in nursing homes and homes for the elderly. Healthy children aged 6 to 24 months, pregnant women, and health care workers in general were not recommended for vaccination. Persons with known anaphylactic hypersensitivity to eggs or its components have a contraindication for vaccination and medical records were scrutinized to exclude such patients. Most Dutch patients have a permanent relationship with the same general practitioner (GP), which enables follow-up of these persons. A search algorithm on encoded information from the medical records was used to select the study subjects.[19] During the study season, 91 practices with 75 227 study patients were included. Of the cohort, 8% were high-risk children and adolescents (age range, 6 months to 17 years; n = 5933), 33% of subjects were high-risk adults (age range, 18-64 years; n = 24 928), and 59% of subjects were 65 years or older (n = 44 366). Decisions concerning diagnosis and treatment of end points were left at the discretion of the GPs. Because study data were supplied anonymously to the data management centers, we did not obtain individual patient consent.

IDENTIFICATION OF CASES AND CONTROLS

Initially, all eligible study subjects were included in the baseline cohort, and all cases and controls were ascertained from this cohort. The nested case-control approach is an efficient alternative to full cohort analysis for the study of drug effects.[20]

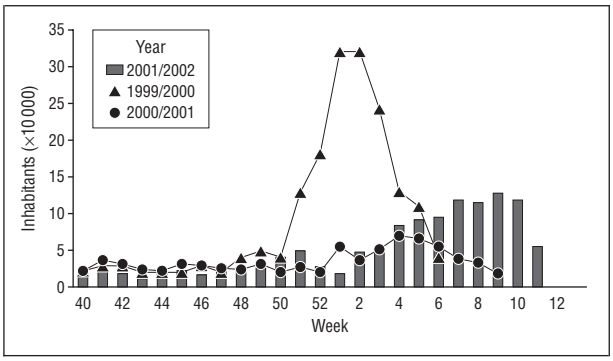

Figure. Influenza activity in the Netherlands, number of influenzalike illnesses per week, per 10 000 inhabitants (1999-2000) (data source: http://www.eiss.org/html/hist_graphs.html; accessed May 1, 2004). Annual influenza surveillance monitoring is conducted by the National Influenza Center in collaboration with the Sentinel Stations, the Netherlands.

During the 1999-2000 influenza A epidemic, an incident case was defined as a person-period of hospitalization because of influenza (*International Classification of Primary Care* [*ICPC*] code [R80]), pneumonia (R81), other acute respiratory disease (acute bronchitis [R78], [exacerbation of] chronic bronchitis [R91], [exacerbation of] emphysema [R95], [exacerbation of] asthma [R96]), acute otitis media (H71), myocardial infarction (K75), congestive heart failure (K77), or stroke (K90), or death from any cause. In addition, GP visits for these diseases were considered as an incident case as well. We scrutinized all medical records (only for the potential cases that had a GP visit that was labeled as an exacerbation of the asthma or chronic obstructive pulmonary disease or congestive heart failure), to see whether a prescription for oral corticosteroids was given for exacerbations or whether a referral took place for heart failure. These additional eligibility criteria were developed to ascertain the more serious events in general practice to avoid selection bias (ie, attendance of the GP is guided by vaccination status).[5] For each possible case identified by a computerized search on *ICPC* codes in April and May after the study season, 4 control persons without an end point were randomly selected by computer from the remainder of that season's baseline cohort. Sampling of controls was conducted within the same age subgroup as the case and during the same season.

Clinical influenza activity was highly epidemic and predominantly associated with influenza A(H3N2) Sydney type during the 1999-2000 season (Figure).[21] The number of patients with influenzalike illness exceeded baseline between weeks 50 of 1999 and 10 of 2000. After review of the medical records of all possible case person-periods, 1920 patients generated 2095 valid case periods. We identified 320 deaths, 192 hospitalizations (30 patients had multiple diagnoses in 1 episode), and 1583 GP visits (23 patients had multiple diagnoses in 1 episode) that fulfilled the eligibility criteria. Valid information on 8593 controls could be retrieved. The case-control ratio was somewhat higher than 1:4, since we originally also defined patients with depression and diabetes events as a potential case. Because there was no evidence for vaccine effectiveness in our data for these end points, we decided to exclude these cases from the final analyses.

ASSESSMENT OF INFLUENZA VACCINATION STATUS

In the Netherlands, virtually all persons recommended for influenza vaccination receive their vaccine from a GP through a standardized vaccination program.[19] Influenza vaccines are free for all recommended persons. Because the GP receives a fee for

Table 1. Baseline Characteristics Estimated From Controls for the Group of High-Risk Children and Adults*

Characteristic	Children Aged 6 mo-17 y (n = 411)			Adults Aged 18-64 y (n = 1778)			Elderly, Age ≥65 y (n = 6404)		
	Unvaccinated (n = 171; 42%)	Vaccinated (n = 240; 58%)	*P* Value†	Unvaccinated (n = 532; 30%)	Vaccinated (n = 1246; 70%)	*P* Value†	Unvaccinated (n = 1207; 19%)	Vaccinated (n = 5197; 81%)	*P* Value†
Age, y	8 ± 5	9 ± 4	.09	42 ± 14	48 ± 12	<.001	74 ± 7	75 ± 7	.03
Male sex	106 (62)	120 (53)	.02	254 (48)	569 (46)	.42	473 (39)	2069 (40)	.69
NHI	82 (48)	148 (62)	.006	339 (64)	878 (71)	.005	815 (68)	3764 (72)	.001
Asthma/COPD	155 (91)	212 (88)	.70	288 (54)	580 (47)	.003	125 (10)	1093 (21)	<.001
Heart disease	1 (1)	8 (3)	.06	74 (18)	299 (24)	.003	321 (27)	2057 (40)	<.001
Diabetes mellitus	2 (1)	0	NA	57 (11)	248 (20)	<.001	132 (11)	891 (17)	<.001
Other disease‡	14 (8)	23 (10)	.84	121 (23)	236 (19)	.07	23 (2)	16 (2)	.48
No. of GP visits§	0.4 ± 0.9	0.6 ± 1.5	.15	0.3 ± 1.3	0.6 ± 1.8	.008	3.7 ± 4.2	2.8 ± 3.8	<.001
No. of prescriptions§	0.4 ± 0.8	0.6 ± 0.9	.02	0.5 ± 1.0	0.6 ± 1.2	.002	0.5 ± 1.2	0.9 ± 1.7	<.001
Specialist care§	12 (7)	25 (10)	.24	41 (8)	166 (13)	.001	96 (8)	739 (14)	<.001
Hospitalization§	2 (1)	4 (2)	.67	5 (1)	26 (2)	.09	19 (2)	164 (3)	.003

Abbreviations: COPD, chronic obstructive pulmonary disease; GP, general practitioner; NA, not assessed; NHI, National Health Insurance.
*Data are given as mean ± SD or number (percentage) of patients unless otherwise specified.
†*P* value comparing vaccinated and unvaccinated persons within age group (<18 and ≥18 years).
‡Other disease: renal disease and immune-related disease.
§In the previous 12 months.

each registered vaccination, we assumed a person to have been vaccinated if the code for influenza vaccination (R44.1) was annotated in the medical records in the period from October 1 to December 7, 1999. In an earlier study during the same season, confirmed exposure or nonexposure to influenza vaccination before the epidemic was in high agreement with the absence or presence of the *ICPC* code for vaccination R44.1 (κ=93%).[5] The trivalent subunit influenza vaccine matched well with circulating influenza A and B strains in the 1999-2000 season.[21]

COVARIATES AND ADJUSTMENT FOR CONFOUNDING BY INDICATION

In line with previous studies from our group and others,[5,7,14,15] prognostic information was obtained from each study subject to be able to adjust for differences in prognosis between vaccinated and unvaccinated subjects.[22] We collected information on the demographic covariates age and sex by means of the earlier mentioned search algorithm.[19] Also, we registered health insurance coverage, which is either a private party insurance or National Health Insurance. The latter is an indicator of a lower social economic status (uninsured status is virtually absent in the Netherlands). Furthermore, we obtained detailed information on the presence of relevant comorbidity (presence of asthma or chronic obstructive pulmonary disease [R91, R95, R96], lung cancer [R84, R85], myocardial infarction [K75], congestive heart failure [K77], other cardiovascular disease [K74, K76, K78, K79, K82-K84], diabetes [T90], chronic renal disease [U88, U99] or immune-related disease [B73, B74, B90]) by medical record review. The numbers of GP visits and medications and referral to a specialist as well as hospitalization for 1 of the possible complications in the 12 months preceding the epidemic were counted and recognized as indicators of disease severity.[15]

SAMPLE SIZE AND DATA ANALYSIS

Prior to the start of the study in September 1999, we used *Epi Info* software (version 6; Centers for Disease Control and Prevention, Atlanta, Ga) to estimate the sample size needed. Based on an earlier study, we expected a vaccination rate of 84%,[5] a case-control ratio of 1:4, and a 2-tailed α level of .05. We assumed to have adequate power of at least 80% to detect an expected odds ratio (OR) for vaccination of 0.7 or lower (ie, effectiveness of ≥30%) if we would be able to include 500 cases and 2000 controls.

Univariate and multivariable logistic regression modeling were used to obtain crude and adjusted ORs and their 95% confidence intervals (CIs) of the association between vaccination and case status in accordance with other reports.[5,7,14,15] The adjusted ORs and their 95% CIs were used as an approximation of the relative risk. The adjusted vaccine effectiveness was calculated as follows: (1−adjusted OR) × 100%.[2,5] We adjusted the vaccine effectiveness estimates by adding the following potential confounders to the regression equation: age, sex, health care insurance, presence of heart or lung disease, and diabetes or other high-risk disease, as well as the number of medications and GP visits and hospitalizations 12 months before the start of the epidemic. We also analyzed the confounding effect of both the dichotomized (0 vs ≥1) and continuous variables GP visits and number of hospitalizations in the previous year in the multivariable analysis, and the results did not change. The same approach was applied to obtain adjusted ORs in each of the 3 primary subgroups. We included a specific subgroup analysis in children younger than 3 years and in high-risk adults aged 50 to 64 years because US recommendations have changed to include healthy persons of these ages.[1] In the analysis concerning adults, we controlled for subgroup and for the fact that some case patients attributed more than 1 person-period using conditional logistic regression analyses and this did not change the findings of unconditional analysis substantially. A 2-sided *P* value less than .05 was considered to indicate statistical significance.

RESULTS

BASELINE CHARACTERISTICS OF CONTROLS

Of 411 high-risk control children and adolescents, 1778 controls aged between 18 and 64 years, and 6404 elderly controls 65 years or older, 240 (58%), 1246 (70%),

Table 2. Incidence Rate* of End Points Per 10 000 Unvaccinated Person-Periods During the 1999-2000 Influenza A Epidemic

Unvaccinated Group at Risk	GP Visit for ARD	GP Visit for CVD	Hospitalization for ARD	Hospitalization for CVD	Death
Children aged <18 y (n = 2683)	339	0	0	0	0
Adults aged 18-64 y (n = 8289)	117	13	8	2	30
Elderly aged ≥65 y (n = 10 288)	155	22	12	24	67

Abbreviations: ARD, acute respiratory disease including acute bronchitis or exacerbations of chronic lung disease, influenza, pneumonia, and acute otitis media; CVD, cerebrovascular disease including myocardial infarction, stroke, and heart failure; GP, general practitioner.

*Incidence rates were calculated as the number of unvaccinated case person-periods within an age subgroup divided by the number of unvaccinated persons at baseline from the same group, multiplied by 10 000.

Table 3. Influenza Vaccine Effectiveness (VE) in Reducing Morbidity and Mortality During the 1999-2000 Influenza A Epidemic

Subgroup	GP Visit for ARD or CVD	Hospitalization for ARD or CVD	Death From Any Cause
High-risk children aged <18 y			
Vaccinated cases, No. (%)	69/160 (43)	3/3 (100)	1/1 (100)
Vaccinated controls, No. (%)	240/411 (59)	240/411 (59)	240/411 (59)
Unadjusted VE (95% CI)	48 (24 to 62)	NA	NA
Adjusted VE (95% CI)	43 (10 to 64)	NA	NA
Adjusted *P* value	.02	NA	NA
High-risk adults aged 18-64 y			
Vaccinated cases, No. (%)	255/363 (70)	14/23 (61)	22/47 (47)
Vaccinated controls, No. (%)	1246/1778 (70)	1246/1778 (70)	1246/1778 (70)
Unadjusted VE (95% CI)	1 (–27 to 23)	59 (–8 to 84)	71 (41 to 86)
Adjusted VE (95% CI)	26 (7 to 47)	87 (39 to 97)	78 (39 to 92)
Adjusted *P* value	.04	.009	.005
Elderly aged ≥65 y			
Vaccinated cases, No. (%)	879/1060 (83)	130/166 (78)	203/272 (75)
Vaccinated controls, No. (%)	5197/6404 (81)	5197/6404 (81)	5197/6404 (81)
Unadjusted VE (95% CI)	0 (–20 to 16)	40 (10 to 49)	43 (23 to 57)
Adjusted VE (95% CI)	7 (–11 to 23)	48 (7 to 71)	50 (23 to 68)
Adjusted *P* value	.42	.03	.002
All adults aged ≥18 y			
Vaccinated cases, No. (%)	1134/1423 (80)	144/189 (76)	225/319 (71)
Vaccinated controls, No. (%)	6443/8182 (79)	6443/8182 (79)	6443/8182 (79)
Unadjusted VE (95% CI)	0 (–16 to 13)	35 (7 to 54)	44 (27 to 56)
Adjusted VE (95% CI)	14 (0 to 26)	55 (24 to 63)	55 (34 to 70)
Adjusted *P* value	.04	.003	<.001

Abbreviations: ARD, acute respiratory disease including acute bronchitis or exacerbations of chronic lung disease, influenza, pneumonia, and acute otitis media; CI, confidence interval; CVD, cerebrovascular disease including myocardial infarction, stroke, and heart failure; GP, general practitioner; NA, not applicable due to low numbers in the outcome category.

and 5197 (81%) persons, respectively, had been vaccinated. Vaccinated subjects were older and showed a higher prevalence of some high-risk diseases compared with unvaccinated subjects (**Table 1**). Also, they were more often insured through the National Health Insurance, indicating a lower socioeconomic status. Among adults, the prevalence of diabetes was higher, and they received more specialist and hospital care. However, the prevalence of other high-risk disease such as immunodeficiency was lower, and they had a lower mean number of GP visits compared with unvaccinated subjects. Among children, vaccinated subjects were more often female. Finally, a higher mean number of medications taken in the 12 months preceding the epidemic was observed in unvaccinated subjects.

END POINTS

Among the 5933 children and adolescents, there was 1 death, 3 hospitalizations, and 160 GP visits. Among 24 928 high-risk adults aged between 18 and 64 years, there were 47 deaths, 23 hospitalizations, and 363 GP visits. Among 44 366 elderly subjects (age ≥65 years), corresponding figures were 272 deaths, 166 hospitalizations, and 1060 GP visits. To explore the impact of influenza in case the cohort would not have been vaccinated, we calculated the incidence rates among unvaccinated persons during the 1999-2000 influenza A epidemic using the baseline cohort (**Table 2**). The incidence rate of all possible complications among the elderly (280 per 10 000) was on average 1.6 times higher than the rate among persons aged between 18 and 64 years (170 per 10 000), and differences in the impact of influenza were most noticeable for the hospitalizations for very serious outcomes for cardiovascular disease and death.

After adjustments for observed differences in baseline risk between vaccinated and unvaccinated high-risk children, GP visits for influenza, pneumonia, acute exacerbations of chronic lung disease, or acute otitis media were prevented by 43% (95% CI, 10%-64%; **Table 3**).

Point estimates for the separate outcomes GP visit for pneumonia or influenza (51%) and acute otitis media (51%) were similar, whereas the point estimate was somewhat lower for asthma exacerbations (25%). Vaccination prevented 78% of deaths (95% CI, 39%-92%), 87% of hospitalizations (95% CI, 39%-97%), and 26% of GP visits (95% CI, 7%-47%) among high-risk persons of working age. Among elderly subjects, the vaccine prevented 50% (95% CI, 23%-68%) of deaths, 48% of hospitalizations (95% CI, 7%-71%), and 7% of GP visits after adjustments, though not statistically significant (95% CI, –11% to 23%). Among all persons 18 years or older, 55% of both deaths and hospitalizations were prevented. Except for the separate outcome hospitalization for congestive heart failure (point estimate of vaccine effectiveness of 18%), corresponding estimates were similar for hospitalizations due to pneumonia or influenza (63%), acute respiratory disease (55%), myocardial infarction (48%), and even somewhat higher for stroke (71%).

Subgroup analysis in the 6- to 24-month age group revealed 50% reduction in GP visits, although the estimate was not statistically significant (95% CI, –94% to 87%). In the group aged between 50 and 64 years, similar point estimates of vaccine effectiveness for all outcomes were observed as in the group aged between 18 and 64 years (GP visits, 38% [95% CI, 7%-58%]; hospitalization, 85% [95% CI, 18%-97%]; and death, 82% [95% CI, 39%-94%]) .

COMMENT

To our knowledge, this study is the first adequately powered analysis, which involved 75 227 observations (30 861 of which were among high-risk persons younger than 65 years), to show that influenza vaccination is highly effective in reducing complications across all age groups. Importantly, the study population from the primary care centers is representative for most persons requiring vaccination according to the guidelines, except for patients from nursing homes or tertiary care.

To appreciate these findings, some issues need to be considered. Because immunization guidelines currently recommend vaccination for patients with high-risk conditions regardless of age,[17] the vaccine effectiveness can no longer be assessed in a placebo-controlled trial.[22,23] The case-control approach used enables the assessments of the effects of vaccination on infrequent severe end points such as hospitalization or death.[5] An advantage of a nested case-control approach includes the reduction of bias due to inappropriate selection of controls. Vaccination rates in controls were similar and comparable with estimates from other large Dutch cohorts.[5,24] Moreover, the distribution of some important characteristics in vaccinated and unvaccinated controls was similar to figures observed in these earlier studies. Furthermore, the potential for recall bias was minimized through the complete review of prospectively collected data in routine medical care from computerized medical records.

Although the GPs were aware of the vaccination status of their patients, it is unlikely to have influenced the diagnostic process in general practice, hence overestimating the true vaccine effectiveness. The GPs have been used to apply the *ICPC* code criteria, which define a certain diagnosis in primary care.[5] Moreover, the GPs were not actively involved in recruiting patients and outcome assessment because the study was performed in the Dutch routine care setting. If such a bias were present, a much higher reduction in the more specific end point (hospitalization and primary care visits for pneumonia or influenza) than in the less specific end points (eg, hospitalization for cerebrovascular disease among adults or GP visits for acute otitis media) would have been expected than what was observed in our study. Obviously, the association of mortality and vaccination status cannot be influenced by such bias, and our vaccine effectiveness point estimate of 50% for the elderly was virtually the same when compared with previous health maintenance organization studies conducted by the group of Nichol et al[2,7] and Hak et al[14] and observed in a meta-analysis by Vu and colleagues.[25]

A major issue in nonexperimental evaluation of vaccines is that by definition unselected vaccinated and unvaccinated patients tend to differ in their prognosis.[22] As shown by the present and previous studies,[5,23,24] the presence of risk factors is higher among vaccinated than among unvaccinated persons, which may have influenced observed associations. However, we minimized this so-called confounding by indication in both the design and data analysis phases of the study.[22] First, we only admitted into the study cohort patients with current indications for vaccination as verified by the GP. Second, because age and presence of high-risk disease are major confounders, we frequency-matched cases and controls on these factors by sampling in subgroups and controlled for their confounding effect in the analyses. Third, we had information on many additional potential confounders and adjusted for these using logistic regression analysis. Obviously, only a large enough randomized controlled trial will fully guarantee absence of confounding, but it is very unlikely that the observed vaccine effectiveness estimates are materially influenced by residual confounding. If so, the reported estimations can only be valued as underestimations because, in general, vaccinated persons run a higher risk for developing an end point compared with unvaccinated persons, as shown in Table 1.[22]

Most studies of the effectiveness of vaccination among the elderly have been restricted to the severe end points (ie, death from all causes or hospitalization for influenza or pneumonia). The assumption is that during influenza outbreaks, influenza is particularly related to the occurrence of these outcomes.[26] However, recent reports have shown that hospital admissions for cardiovascular[6,7,27] and cerebrovascular[7,28] complications may also be reduced by vaccination. Our study confirms these observations.

Some might argue that in our study, as in all large-scale observational studies, virological analysis of (a sample of) our cases to detect influenza infection was not performed.[29] Therefore, part of the complications may not have been caused by the influenza virus. As a consequence, if anything, vaccine effectiveness estimates tend to underestimate the true reductions from vaccina-

tion.[2,30] We were not able to retrospectively verify whether case ascertainment was complete. However, occurrence rates of pneumonia, acute cardiac disease, and death among unvaccinated subjects of working age in the 1999-2000 influenza A season were comparable to data from a previous study among a smaller group of patients with chronic pulmonary disease followed up during influenza epidemics.[5] Also, the incidence rates of hospitalization for pneumonia and influenza and all-cause mortality among the elderly subjects were similar to findings in the United States.[14,30]

Only few studies have been conducted among children and adolescents with chronic high-risk disease, and these tended to be small. In a vaccine trial among 696 asthmatic children and adolescents aged between 6 and 18 years, influenza-related asthma exacerbations were of similar severity in both the vaccine and placebo groups, but they lasted 3.1 days less in the vaccine group (95% CI, –6.2 to 0.002 days; $P = .06$).[31] The authors concluded that influenza vaccination did not result in a significant reduction of the number, severity, or duration of asthma exacerbations caused by influenza. However, the incidence of influenza-related asthma exacerbations was very low, hence the power of that study appeared inadequate to estimate reductions in outcomes of 35% or less. In a nonexperimental study including infants and younger children, the vaccine reduced the occurrence of episodes of otitis media by 36%.[32] The number of febrile influenza A episodes was reduced by 68%[33] in a study among children, and acute respiratory disease was reduced by 55% among children with asthma in a previous small cohort study by our group.[34] In the present study, we observed a 43% reduction in GP visits for acute respiratory disease and acute otitis media during the 1999-2000 influenza epidemic, an estimate that is in accordance with most of these earlier small-scale studies. However, we lacked adequate power to establish a potential association between vaccination status and the more severe end points (ie, hospitalization or death) among these children.

To our knowledge, this is the first study showing high vaccine effectiveness in reducing severe end points such as deaths (78%) and hospitalizations for acute respiratory and cardiovascular disease (87%) among high-risk persons of working age. As yet, the Cochrane Collaboration has not found any evidence for effectiveness of vaccination among adults with asthma.[35] In a smaller case-control study among younger adults with asthma or chronic obstructive pulmonary disease, we found influenza virus in 55% of the exacerbations in the same season.[5] However, we were not able to detect reductions in GP visits for acute respiratory disease, most probably because of inadequate power of the study size. In the present study, 26% of GP visits appeared to be prevented during the influenza epidemic, which is in accordance with 23% reduction in primary care visits as observed among elderly patients with chronic pulmonary disease.[36] In a large-scale cohort study among elderly patients of 3 health maintenance organizations, it was shown that the relative risk reduction by influenza vaccination was not modified by the presence of certain high-risk medical conditions.[14,37] Our data indicate that younger age also does not modify the clinical effectiveness.

Vaccination rates among high-risk patients younger than 65 years, most of them with chronic lung disease, are lagging far behind the health objectives of many countries including the United States[1] and the Netherlands.[5] Recently, the American Lung Association has convincingly demonstrated that influenza vaccination is not associated with severe adverse effects among patients with asthma.[38] From a medical point of view, we have demonstrated that the clinical benefits of vaccination outweigh the possible adverse effects, and there seem to be no barriers to have these younger persons vaccinated. However, from a cost-effectiveness point of view, it is important to bear in mind that the vaccine can only be effective, hence saving costs, during a season with considerable influenza activity and if the vaccine matches the circulating strains.[18] A cost-effectiveness analysis incorporating these uncertainties is therefore urgently needed.

In conclusion, the results of our study lend strong support for the view that all high-risk persons benefit from annual influenza vaccination regardless of age. Therefore, efforts should be renewed to convince providers and patients of the clinical usefulness of such vaccination, notably among younger high-risk persons.

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