Conventional Influenza Vaccination Is Not Associated with Complications in Working-Age Patients with Asthma or Chronic Obstructive Pulmonary Disease

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By using a nested case-control design, the authors studied the effectiveness of the influenza vaccine in reducing severe and fatal complications in 4,241 and 5,966 primary care, working-age patients aged 18–64 years who had asthma or chronic obstructive pulmonary disease during the 1998–1999 and 1999–2000 influenza epidemics in the Netherlands. Patients developing fatal or nonfatal exacerbations of lung disease, pneumonia, congestive 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. Conditional logistic regression and propensity scores were used to assess vaccine effectiveness after adjustment for confounding factors. In seasons one and two, respectively, 87% (47/54) and 85% (171/202) of the cases and 74% (155/210) and 75% (575/766) of the controls had been vaccinated. After adjustments, vaccination was not associated with reductions in complications (season one: odds ratio = 0.95, 95% confidence interval (CI): 0.26, 3.48; season two: odds ratio = 1.07, 95% CI: 0.59, 1.96; pooled odds ratio = 1.07, 95% CI: 0.63, 1.80). Because influenza vaccination appeared not to be associated with a clinically relevant reduction in severe morbidity, other measures need to be explored.

case-control studies; immunization; influenza; lung diseases; middle age; vaccines

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease.

The risk of influenza-related morbidity and mortality during influenza epidemics is high (1–4), and nonexperimental studies have shown that vaccination against influenza prevents respiratory and cardiac complications during epidemics in elderly patients with chronic obstructive pulmonary disease (COPD) (5, 6). However, relatively little information is available regarding working-age patients with COPD. Some studies have shown 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 suggest a relatively minor role for influenza (10, 11). Although the vaccine does not lead to potentially adverse effects in asthmatics (12), the few available small-scale studies on the clinical benefits of influenza vaccination among working-age patients with COPD

have failed to demonstrate any effectiveness from annual vaccination (6, 13, 14).

We determined the occurrence of respiratory and cardiac morbidity during influenza periods and the clinical effectiveness of vaccination in reducing these complications in patients aged 18–64 years who had asthma or COPD by using a prospective, nested case-control design. Our observations covered the 1998–1999 influenza outbreak (principally type B) and the 1999–2000 epidemic (mainly type A (H3N2)) (15, 16). Since it is well known that influenza causes only part of the complications and that our outcome might therefore be nonspecific, as was the case in many previous reports (3–6), we also obtained nose and throat swabs from a sample of cases and controls to assess the relative contribution of influenza to complications.

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MATERIALS AND METHODS

Source population

Study subjects were chosen from among primary care patients aged 18–64 years who had asthma or COPD and had been 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 during the 1998–1999 influenza epidemic, and 93 general practitioners in 52 centers participated during the 1999–2000 epidemic. These general practitioners routinely integrate all patient information in text format or encoded in their computerized records by using the General Practitioners Information System ELIAS (Torex-Hiscom, Houten, the Netherlands) (19).

Patients eligible for inclusion in 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 age and the presence of COPD, as indicated by International Classification of Primary Care diagnostic codes (R91, R95, R96), Anatomical Therapeutic Classification medical drug codes (class R03), and a tag in their computerized records indicating COPD. Next, the general practitioners were asked to verify whether the diagnosis of asthma or COPD in the preselected patients had been made in accordance with the Dutch College of General Practitioners guidelines (21). In October 1999 and October 2000, 4,241 and 5,966 eligible patients of a total of 6,011 and 8,495 study patients, respectively, preselected by using the search algorithm in the general practitioner information systems, were enrolled.

Since all data were supplied anonymously to the Julius Center for Health Sciences and Primary Care (Utrecht, the Netherlands), individual patient consent was not obtained. 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 cases if they had a primary diagnosis of an episode of fatal or nonfatal severe exacerbation of underlying lung disease, pneumonia, congestive heart failure, or myocardial infarction during either epidemic (refer to the Appendix). Case criteria were verified by using a computerized questionnaire, which was integrated in the medical records of study patients and could be activated by their general practitioners 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 the weeks in which the incidence of influenza-like illness reported by the sentinel practices was more than four per 10,000 inhabitants per week (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 biphasic influenza outbreak, the influenza B-Harbin-type virus predominated, followed by a smaller wave of A(H3N2)Sydney. Clinical influenza activity during the 1999–2000 season was predominantly associated with influenza type A(H3N2)Sydney.

In seasons one and two, six of 60 and five of 207 cases, respectively, were deemed ineligible for the study because it was unclear whether they had asthma or COPD; therefore, these patients and their controls were excluded from further consideration. In addition, 47 and 174 patients with severe exacerbation of asthma or COPD, five and 26 patients with pneumonia, zero and one patient with congestive heart failure, and two and one patient who died, respectively, were considered eligible cases. No myocardial infarctions were recorded. In seasons one and two, eight and 16 cases, respectively, were hospitalized.

Identification of controls

Each time that a case was identified, we randomly selected four controls from the remainder of that season's cohort, matched by age (in the same 5-year age category) and sex. Of the 1,024 controls selected from the database, 50 were excluded because either no data were available for them or the baseline diagnosis was unclear or they had died or had been lost to follow-up before the relevant epidemics occurred.

Assessment and confirmation of exposure to influenza vaccine

In the Netherlands, almost all persons receive the influenza vaccine through a primary care vaccination program (17). In both seasons, the composition of the trivalent subunit influenza vaccine complied with World Health Organization recommendations and matched well with circulating influenza A and B strains, as quantified by high hemagglutinin inhibition titer in ferret sera (15, 16). A person was assumed to have been vaccinated if his or her general practitioner retrospectively confirmed receipt of influenza vaccination by reviewing the medical records. Confirmed exposure/nonexposure to influenza vaccination within the 2 months before either epidemic was in high agreement with the absence/presence of the International Classification of Primary Care R44.1 code for vaccination (kappa = 0.93).

Measurements of covariates

Baseline demographic information, including age, sex, and health insurance coverage (private or National Health Service), was collected by using the software module (20). These data are required by health insurance companies and are therefore valid and reliable. Further detailed information was obtained on potential risk factors by review of medical records by the participating general practitioners, who were unaware of the role of these covariate assessments in relation to the primary aim of the study. We extracted information on the presence of concomitant high-risk disease and previous hospital admissions in the 12 months preceding the epidemic. In addition, influenza infection and influenza vaccination status in the previous season and chronic use of medications

were registered, and the numbers of consultations in the preceding year were counted as an indicator of disease severity and use of medical services. Some of the cases and controls in the second, 1999–2000 season (608 of 1,012) participated in an additional questionnaire study (unpublished data). Kappa values, as a measure of agreement between patient and general practitioner information, were satisfactory for some important variables: 0.64 for the presence or absence of chronic comorbid disease, 0.54 for the presence or absence of respiratory medication use, and 0.54 for the presence or absence of previous influenza vaccination.

Virology

Six primary care centers that included 23 trained general practitioners from the Utrecht academic network (6) were asked to take nose and throat swabs from their cases and from a sample of controls for virologic assessment. Specimens were put into 4 ml of transport medium. Swabs were vortexed for 10 seconds and were centrifuged at $2,000 \times g$ for 15 minutes. One ml of the supernatant was used directly for rapid virus culturing and antigen testing by immunofluorescence with monoclonal antibodies against influenza virus. 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 syncytial virus; picornaviruses (rhinovirus and enterovirus); parainfluenza 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 allowing for nonspecificity, as observed in other studies) (3–5). We assumed 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 vaccine effectiveness independent of confounding factors. In the modeling procedure, factors that appeared to be strongly associated with both exposure to vaccination and case status were first added to the naive model that included 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). Although it has been shown that vaccine uptake is determined by patient rather than practice or physician factors (24), we extended the analysis by matching by practice, which did not materially change the results. Since circulating viruses and vaccination components differed in the two seasons and only a minority of subjects were admitted to the study during both seasons, we pooled the observations and performed similar analyses on case and control person-periods (25). Moreover, we decided in advance to use statistical interaction terms to determine potential modification of vaccine effectiveness by age (18–39, 40–64 years), sex, disease (asthma or COPD),

and care by a pulmonologist. Adjusted odds ratios, as approximations of relative risks, and their 95 percent confidence intervals were calculated.

Second, we applied the propensity score method, a recently introduced, powerful method of further removing "confounding by indication" (26, 27). This technique enables assessment of the association of an intervention, that is, vaccination, with outcomes in patients who have an equal probability of receiving the vaccine. 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 that included age and sex, health insurance, underlying disease, use of prednisolone and inhaled corticosteroids, specialist care, and cardiac and other comorbidity was appropriate (Hosmer-Lemeshow goodness-of-fit test: $p = 0.41$), and the model's discriminative ability was moderate to good, with a value of 0.71 (95 percent confidence interval (CI): 0.68, 0.75) for the area under the receiver operating curve. In a patient-matching procedure, we searched for a vaccinated person who had a propensity score closest (within a range of 0.00–0.01) to that for each unvaccinated patient. Thus, in this quasi-experiment, two comparison groups that had an equal probability of vaccination were formed, and, in an analogy to the analysis of trials, cumulative incidences of complications were compared.

RESULTS

The overall cumulative incidence of complications—mainly respiratory—was 13 per 1,000 in the first season and 34 per 1,000 in the second season (table 1). Influenza morbidity was highest in the older age group (45–64 years), in females, and in those subjects who had COPD.

Vaccinated subjects were older and had a higher prevalence of COPD and of cardiac and other comorbidity, and they were more often insured through the National Health Service than were unvaccinated subjects (table 2). In addition, vaccinated subjects had higher general practitioner consultation and hospitalization rates in the 12 months preceding baseline and had more often been vaccinated against influenza in the previous season.

Eighty-seven percent of cases and 74 percent of controls had been vaccinated in season one compared with 85 percent of cases and 75 percent of controls in season two (table 3). After we adjusted for the matching variables age and sex and for potential confounders, we found that the vaccine apparently was not associated with any reduction in the incidence of complications (season one: odds ratio = 0.95, 95 percent CI: 0.26, 3.48; season two: odds ratio = 1.07, 95 percent CI: 0.59, 1.96; pooled odds ratio = 1.07, 95 percent CI: 0.63, 1.80). In addition, vaccine effectiveness was not significantly modified by age, sex, or underlying pulmonary disease or by care received from a pulmonologist.

In the propensity score analysis, outcome rates for the 257 vaccinated and 257 unvaccinated subjects who had been matched on their equal probability of being vaccinated were

TABLE 1. Cumulative incidence (per 1,000) of influenza-associated morbidity and mortality by age, sex, and pulmonary disease during two influenza seasons in the Netherlands

Characteristic	1998–1999 influenza epidemic (n = 4,241)				1999–2000 influenza epidemic (n = 5,966)			
	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
Pulmonary 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

* COPD, chronic obstructive pulmonary disease.
† Death (two in the 1998–1999 season, one in the 1999–2000 season) or congestive heart failure (one case in the 1999–2000 season).

equal (relative risk = 1.03, 95 percent CI: 0.66, 1.62; refer to table 4).

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

DISCUSSION

This study showed that, although influenza-associated respiratory morbidity is common among working-age patients who have asthma or COPD, no evidence exists that the annual, conventional, inactivated trivalent subunit influenza vaccine reduces the incidence rate of these complications. Since many immunization guidelines recommend influenza vaccination for patients with asthma or COPD, vaccine effectiveness cannot be assessed in a placebo-

TABLE 2. Characteristics of study subjects at baseline and during influenza seasons (estimated from controls) according to vaccination status,* the Netherlands

Characteristic	1998–1999 baseline cohort influenza season			1998–1999 influenza season			1999–2000 influenza season		
	Vaccinated (n = 2,687)	Unvaccinated (n = 1,414)	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 (years)	44.3	37.3	<0.001	51.2	48.2	0.06	51.6	45.4	<0.001
Male sex (%)	43.8	49.7	0.001	50.3	44.4	0.43	49.5	55.4	0.15
National Health Service insurance (%)	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 (%)‡									
≥4 general practitioner visits				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
Inhalation of corticosteroids				63.9	57.1	0.35	59.4	42.1	<0.001
Use of oral corticosteroids				16.3	4.8	0.022	18.3	7.4	<0.001
Use of bronchodilators				59.2	60.3	0.83	64.2	46.5	<0.001

* International Classification of Primary Care code R44.1 was used as an indicator of vaccination status; patient records were not reviewed for the total baseline cohort (n = 4,241).
† COPD, chronic obstructive pulmonary disease.
‡ Use in the 12-month period before October 1999 or 2000.

TABLE 3.   Influenza vaccination and risk of influenza-associated complications, the Netherlands, 1998–1999 and 1999–2000

Influenza vaccination	Cases (%)	Controls (%)	Adjustment	Adjusted odds ratio*	95% confidence interval
1998–1999 influenza epidemic	$n = 54$	$n = 210$			
Influenza vaccine prior to the 1998–1999 epidemic	87	74	Age and gender (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 use	0.94	0.31, 2.83
			+ 7 remaining factors†	0.95	0.26, 3.48‡
1999–2000 influenza epidemic	$n = 202$	$n = 766$			
Influenza vaccine prior to the 1999–2000 epidemic	85	75	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 use	1.09	0.60, 1.97
			+ 7 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	75			

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

† Disease (asthma/chronic obstructive pulmonary disease), health insurance, general practitioner visits, 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, $p = 0.93$.

controlled trial. The case-control approach enables assessment of the effects of vaccination on severe endpoints for which incidence is relatively low. An advantage of the nested case-control study includes reduction of bias due to inappropriate selection of controls. Exposure rates in controls were similar in both seasons and were comparable with those in the baseline cohort. Although the controls were somewhat older than the total cohort, the distribution of

TABLE 4.   Baseline characteristics and outcome of the influenza vaccination study in which the propensity score was used ($n = 514$), the Netherlands, 1998–1999 and 1999–2000

Characteristic	Vaccinated ($n = 257$)		Unvaccinated ($n = 257$)		p value of difference
	No.	%	No.	%	
Mean age (years)	45.9		45.7		0.83
Male sex	141	54.9	129	50.2	0.29
National Health Service insurance	148	57.6	150	58.3	0.86
COPD*	80	31.1	75	29.2	0.63
≥4 general practitioner visits	12	4.7	19	7.4	0.19
Cardiac comorbidity	3	1.2	2	0.8	0.65
Other high-risk disease	8	3.1	8	3.1	1.0
Previous hospitalization	3	1.2	7	2.7	0.20
Inhaled corticosteroids	136	52.9	125	48.6	0.33
Oral corticosteroids	20	7.8	26	10.1	0.35
Bronchodilators	152	59.1	139	54.1	0.25
Treatment by pulmonologist	29	11.3	29	11.3	1.00
Influenza in the previous season	32	12.5	34	13.2	0.79
Outcome†					
Exacerbation	30	37.0	31	38.3	0.91
Pneumonia	3	3.7	1	1.2	0.25
All complications	33	12.8	32	12.5	0.89

* COPD, chronic obstructive pulmonary disease.

† Outcomes of the two influenza seasons combined.

TABLE 5. Viral etiology of complications during the 1998–1999 influenza B and 1999–2000 influenza A epidemics in the Netherlands

Viruses	1998–1999 influenza epidemic (n = 56)*				1999–2000 influenza epidemic (n = 44)†			
	Cases (n = 22)		Controls (n = 34)		Cases (n = 20)		Controls (n = 24)	
	No.	%	No.	%	No.	%	No.	%
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
Rhinovirus	2	9	0	0	2	10	1	4
Coronavirus	1	5	0	0	2	10	1	4
Enterovirus	0	0	0	0	0	0	0	0
Respiratory syncytial 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.

some important characteristics in vaccinated and unvaccinated controls was comparable with that in the baseline cohort. Furthermore, potential recall bias was minimized by using computerized medical records.

Several potential limitations of our study need to be considered. A major issue in nonexperimental evaluation of vaccines is often that vaccinated and unvaccinated patients are not prognostically comparable. As expected, and as shown in the present and previous studies, vaccinees have more risk factors than nonvaccinees (4–6, 25, 28). This fact may have obscured a positive effect of vaccination. However, we minimized this so-called confounding by indication in both the design and data-analysis phases of the study (23). First, we admitted into the study cohorts only those patients who had 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 (29, 30). Second, since age and sex are major confounders, we matched cases and controls for these factors. In addition, matched analysis by general practice did not change our results. Third, we had information on many potential confounders, and we adjusted for them by using 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 (26, 27). Although the statistical power of the latter approach was more limited, risk factors were apparently distributed similarly in the selected vaccinated and unvaccinated subjects, and no difference was found in the incidence 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 nonexperimental study could be explained by residual confounding in our data.

Most studies of the effectiveness of vaccination in the elderly have been restricted to even more severe endpoints such as death or hospitalization for influenza or pneumonia, assuming that, during influenza outbreaks, the influenza is frequently a causal component of these outcomes (31, 32). 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 settings or at outpatient clinics (refer to the Appendix). For example, Rothbarth et al. (14) estimated that, in the Netherlands, 11 excess deaths occur in this group of half a million persons during influenza epidemics. In other words, if the vaccine could prevent 50 percent of the deaths (5), more than 100,000 patients would need to be vaccinated to prevent one death. A major strength of our study is that virologic 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 those reported in earlier influenza studies in this age group (10, 11). Furthermore, in season one, which was predominated by influenza B types, most of the positive cases had influenza A infection. This finding accords with ours and findings from others that the incidence of cases was much lower in this season compared with the influenza A season. We were not able to verify retrospectively whether case ascertainment was complete. However, occurrence rates of pneumonia, acute cardiac disease, and death in the 1999–2000 influenza A season were comparable with data from a previous study in a smaller group of similar patients followed up during the 1995–1996 influenza A epidemic (6).

Although a positive relation between respiratory virus infections and exacerbations of asthma has been well established, the etiologic role of influenza viruses has long been underestimated. The underestimated role of influenza might mainly be due to the laboratory techniques used to detect these viruses; in recent years, polymerase chain reaction has become available for rapid diagnosis of influenza infection,

considerably increasing diagnostic accuracy compared with conventional virologic analysis (22, 33).

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 in 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. Since more than 500,000 working-age patients with asthma or COPD are currently indicated for influenza vaccination at a cost of 7 million euros (approximately $13 million) annually, we are convinced that, from a cost-effectiveness point of view, lower than 35 percent reductions in severe outcomes as a result of vaccination do not justify such a costly, large-scale campaign. Other less severe endpoints such as productivity loss or minor exacerbations might be reduced by vaccination, although it is unlikely in light of our results. However, from a public health perspective, such possible benefits might also not justify this preventive program.

Our finding of a lack of benefit from influenza vaccination in respiratory patients of working-age corroborates some earlier observations. For example, Paul et al. (34) observed no reduction in acute respiratory illness in a small subset of vaccinated high-risk patients less than 65 years of age during the 1985–1986 influenza epidemic. Stenius-Aarniala et al. (35) also found no protective effect of the vaccine in reducing asthma exacerbations in a randomized controlled trial among asthmatics, although influenza activity during the follow-up period was low. Wiselka et al. (36) 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.

These observations seem counterintuitive 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 working-age patients with asthma or COPD against influenza (18). Although the occurrence of endpoints was twice as high in COPD patients compared with asthmatics in our study, the vaccine did not reduce the incidence of endpoints in either group. It is still unclear why the vaccine is clinically not effective in both patient groups less than age 65 years. One possible explanation could be that virus-induced allergy and hyperreactivity as precipitating factors may be a much more significant pathologic mechanism in adults than in young children and the elderly (11, 37, 38). If this explanation is true, preventive measures other than vaccination against influenza, such as self-management programs aimed at reducing the 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.

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(*Appendix follows.*)

APPENDIX

APPENDIX TABLE 1. Definition of cases in the study of the association of conventional influenza vaccination with complications in working-age patients with asthma or chronic obstructive pulmonary disease, the Netherlands, 1998–1999 and 1999–2000

Respiratory illness	Cardiac illness	Death
Severe exacerbation of asthma/COPD*	Congestive heart failure	
At least 1 of 4 criteria:	At least 1 of 2 criteria:	At least one criterion:
Confirmation by a pulmonologist	Confirmation by a cardiologist	Primary cause of death, influenza; exacerbation of asthma/COPD, pneumonia, congestive heart failure, myocardial infarction
FEV_1* <60% predicted	≥3 signs and symptoms and prescription of furosemide:	Sudden cardiac death (<1 hour after first symptoms, and cardiac cause not excludable)
PEF* <70% of personal best	Edema	
≥3 signs and symptoms, or ≥2 signs and symptoms and use of oral corticosteroids:	Increased central venous pressure or hepatomegaly	
Insufficient recovery	Signs of pulmonary congestion or hydropneumothorax	
Expiratory wheezing	Enlarged heart	
Cough	Dyspnea	
Increased dyspnea	Myocardial infarction	
Insomnia	At least 1 of 2 criteria:	
Sputum production	Confirmation by a cardiologist	
Exhaustion	≥ 2 signs and symptoms for <8 weeks:	
Pneumonia (with or without influenza)	Angina (>15 minutes) indicating myocardial ischemia	
Presence of at least one criterion:	Abnormal ST-T changes or Q-elevations on ECG*	
Confirmation by radiography	Increased heart enzymes	
≥3 of the following signs and symptoms:		
Decreased intensity of breath sounds		
Dullness on chest percussion		
Inspiratory crackles		
Bronchophony		
Fever (≥38°C)		
Local chest pain on deep inhalation		

* COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; PEF, peak expiratory flow; ECG, electrocardiogram.