

# Clinical Effectiveness of First and Repeat Influenza Vaccination in Adult and Elderly Diabetic Patients

INGRID LOOIJMANS-VAN DEN AKKER, MD<sup>1</sup>  
THEO J.M. VERHEIJ, MD, PHD<sup>1</sup>  
ERIK BUSKENS, MD, PHD<sup>1</sup>

KRISTIN L. NICHOL, MD, MPH, MBA<sup>2</sup>  
GUY E.H.M. RUTTEN, MD, PHD<sup>1</sup>  
EELKO HAK, MSC, PHD<sup>1</sup>

**OBJECTIVE**— Influenza vaccine uptake remains low among the high-risk group of patients with diabetes, partly because of conflicting evidence regarding its potential benefits. We assessed the clinical effectiveness of influenza vaccination in adults with diabetes and specifically examined potential modification of effect by age and prior influenza vaccine uptake.

**RESEARCH DESIGN AND METHODS**— The study was part of the Prevention of Influenza, Surveillance and Management (PRISMA) study, a nested case-control study conducted during the 1999–2000 influenza A epidemic, among 75,235 patients from primary care of any age recommended for vaccination. Among 9,238 adult patients with diabetes, 131 cases arose who were either hospitalized for diabetes dysregulation, acute respiratory disease, or cardiovascular disease and 61 cases who died, and we compared them with 1,561 control subjects. We evaluated the effect of (prior) influenza vaccination by means of logistic regression analysis controlling for age, sex, health insurance coverage, prior health care use, medication use, and comorbid conditions.

**RESULTS**— Vaccination was associated with a 56% reduction in any complication (95% CI 36–70%), a 54% reduction in hospitalizations (26–71%), and 58% reduction in deaths (13–80%). Among study subjects aged 18–64 years, we observed somewhat higher reductions in the occurrence of any complication than among those aged >65 years (72 vs. 39%). In first-time vaccinated subjects, the primary end point was reduced by 47% (0.2–72%), and in those who received vaccination in the year before, the reduction was 58% (4–81%).

**CONCLUSIONS**— Adults with type 2 diabetes, like other individuals from recognized risk groups, benefit considerably from influenza vaccination, and no difference in vaccine effectiveness was observed between first-time and repeat vaccination.

*Diabetes Care* 29:1771–1776, 2006

Patients with diabetes are at high risk for developing a complicated course from lower-respiratory tract infections (1); hence, annual influenza vaccination has been recommended for decades in these individuals (2,3). Despite these long-term recommendations, in the 2004–2005 influenza season, vaccination levels still remained much lower

than the 2010 health objectives in the U.S. vaccination coverage (only 25.5% in the high-risk adult group [18–64 years of age] and 62.7% in all individuals ≥65 years of age) (4). One of the major reasons might be that evidence regarding the clinical benefits of such vaccination is conflicting, and protection has been questioned because of a potential de-

creased T-cell-mediated immune response (5).

Several experimental studies did not observe differences in serological protection against influenza infection by vaccination between patients with diabetes and healthy control subjects (Table 1) (6–9). However, only few studies aimed to establish effectiveness of influenza vaccination against serious morbidity and mortality in diabetic patients, and results of these studies are inconsistent. Colquhoun et al. (10), for example, observed that influenza vaccination reduced hospital admissions of diabetic patients during an influenza epidemic by 79%. Hak et al. (11) also found significant vaccine effectiveness among the subgroup of elderly individuals with diabetes with reductions in hospitalization for influenza or pneumonia or death from any cause ranging from 50% in one influenza season to 21% in the second season. In contrast, Heymann et al. (12) did not find clinical effects of such vaccination in the subgroup of elderly individuals with diabetes.

The primary objective of our study was to determine the effectiveness of influenza vaccination in reducing the occurrence of hospitalization and death from any cause in adults with diabetes during an influenza epidemic.

## RESEARCH DESIGN AND METHODS

The design of the primary care-based Prevention of Influenza, Surveillance and Management (PRISMA) nested case-control study has been described elsewhere (13). Previously, we have demonstrated that a nested case-control approach is an efficient alternative to full-cohort analysis for the study of influenza vaccination (14). The PRISMA study was conducted in 91 general practices during the 1999–2000 influenza A epidemic and during two consecutive seasons in which the influenza activity appeared virtually absent (the 2000–2001 season) or mild (the 2001–2002 season). For the purpose of our study, we therefore choose to analyze the data of case and control subjects ascertained from the primary care-based cohort of 75,235 study patients of any age followed up during the

From the <sup>1</sup>Julius Center for Health Sciences and Primary Health Care, University Medical Center, Utrecht, the Netherlands; and the <sup>2</sup>Veterans Affairs Medical Center, Minneapolis, Minnesota.

Address correspondence and reprint requests to Dr. E. Hak, University Medical Center Utrecht, Julius Center for Health Sciences and Primary Health Care, HP 6.139, P.O. Box 85060, 3508 AB Utrecht, Netherlands. E-mail: e.hak@umcutrecht.nl.

Received for publication 22 December 2005 and accepted in revised form 16 May 2006.

K.L.N. has served on an advisory board for and received consulting fees from GlaxoSmithKline.

**Abbreviations:** GP, general practitioner; ICPC, International Classification of Primary Care; PRISMA, Prevention of Influenza, Surveillance and Management.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc05-2517

© 2006 by the American Diabetes Association.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Table 1—Characteristics of influenza effectiveness studies in individuals with diabetes

Authors	Study type	Influenza season	End points	Conclusion
Serological studies				
Pozilli et al.	Case-control	1984–1985	Postvaccination antibody titer and cell-mediated immune response in adults with type 1 or type 2 diabetes compared with healthy control subjects	No significant difference
Diepersloot et al.	Case-control	1987–1988	Postvaccination antibody titer in adults with type 1 diabetes compared with healthy control subjects	No significant difference
McElhanev et al.	Case-control	1993–1994	Pre- and postvaccination in vitro challenge of peripheral blood mononuclear cells with live influenza virus, measuring interleukin-2 activity in elderly (aged $\geq 60$ years) with type 2 diabetes compared with healthy control subjects	Increased postvaccination interleukin-2 production in diabetic patients due to vaccination history; no difference due to diabetes
Feery et al.	Case-control	1980–1981	Postvaccination antibody titer in adults with type 1 or type 2 diabetes compared with healthy control subjects	No significant difference and influenza vaccination is safe
Clinical studies				
Colquhoun et al.	Case-control	1989–1990 and 1993	Hospitalization for influenza, pneumonia, bronchitis, diabetic ketoacidosis, coma, or diabetes in people of all age-groups with type 1 or type 2 diabetes compared with control subjects with type 1 or type 2 diabetes	79% reduction in hospitalization
Heymann et al.	Case-control	2000–2001	Hospitalization in internal medicine and geriatric wards for any reason or death in elderly (aged $\geq 65$ years) with type 1 or type 2 diabetes compared with healthy control subjects	23% reduction in hospitalization and death among elderly patients; no additional benefit for diabetic patients
Hak et al.	Case-control	1996–1997 and 1997–1998	Hospitalization for pneumonia/influenza or death in people aged $\geq 65$ years with type 1 or type 2 diabetes compared with healthy control subjects	31–48% reduction in hospitalization and death in high-risk elderly and 21%–50% reduction in people with diabetes

1999–2000 influenza A(H3N1) epidemic for the original and present study. Among the original cohort of patients who were all eligible for annual influenza vaccination according to guidelines of the Dutch Health council, 9,238 adult patients had a primary care diagnosis of diabetes (44% aged 18–64 years and 56% aged  $\geq 65$  years). Influenza vaccine uptake among this subcohort was high (81%). Since study data were supplied anonymously to the data-management centers, we did not obtain individual patient consent.

**Identification of case and control subjects**

Patients with diabetes were defined as an incident case when a person-period of

physician-diagnosed influenza (International Classification of Primary Care [ICPC] code [R80]), pneumonia (R81), other acute respiratory disease defined as acute bronchitis (R78), prednisolone-treated chronic bronchitis (R91), emphysema (R95) or asthma (R96), myocardial infarction (K75), congestive heart failure (K77), stroke (K90), diabetes dysregulation (T90) requiring hospitalization, or death from any cause was present. According to the ICPC coding classification, coding for influenza requires a positive test for the presence of influenza. Coding for pneumonia requires either a positive X-ray or at least three of six clinical criteria suggestive of pneumonia (reduced breathing frequency, dull percussion, lo-

cal crepitations, bronchophony, temperature  $>38^{\circ}\text{C}$ , and thorax pain). The coding of heart failure requires confirmation by a cardiologist or at least three of five symptoms suggestive of heart failure (edema, increased central venous pressure, pleural signs, enlarged heart, and dyspnoea). The diagnosis of stroke is made by a specialist. For exacerbations of chronic pulmonary disease, no coding is available. As in a previous study from our group, we only selected those patients who were coded for their pulmonary disease in combination with a treatment with oral prednisolone. Serious diabetes dysregulation requiring hospitalization is defined in Dutch primary care guidelines as hyperglycemia  $>20$  mmol/l. Because of a

Downloaded from <http://diabetesjournals.org/care/article-pdf/29/8/1771/593646/zdc000806001771.pdf> by guest on 25 September 2023

high diagnostic uncertainty in primary care, we only included patients diagnosed in hospital and those who died from any cause. Control patients with diabetes did not have an end point and were randomly selected from the remainder of the baseline cohort (15). Since we studied a subgroup of the original study in which the case-control ratio was  $\sim 1:4$ , we had more control subjects available per case in the present analysis.

Clinical influenza activity during the 1999–2000 season was highly epidemic from week 50 in 1999 to week 10 in 2000 and predominantly associated with influenza A(H3N2) Sydney type (16).

### Assessment of first and repeat influenza vaccination

In the Netherlands, influenza vaccination is administered free of charge by the general practitioner (GP) to most individuals recommended for influenza vaccination through the national influenza vaccination program. GPs receive a fee for each registered vaccination. We assumed that an individual had been vaccinated for the present study season if the code for influenza vaccination (R44.1) was recorded in the period from 1 October 1999 to 7 December 1999. We also recorded whether the patient had received the vaccine in the same period in the year before (1998). Those who did not receive the vaccine that year were designated “first vaccinated subject” and others as “repeat vaccinated subject.” An earlier study during the same season confirmed that exposure/nonexposure to influenza vaccination before the epidemic was in high agreement with the absence/presence of the ICPC code for vaccination R44.1 ( $\kappa$  93%) (17). The trivalent subunit influenza vaccine matched well with circulating influenza A and B strains in the 1999–2000 season (16).

### Covariates and adjustment for confounding by indication

We obtained prognostic information from each study subject to be able to adjust for differences in prognosis between vaccinated and unvaccinated subjects (17–19,20). Information was collected on a number of covariates while accounting for age and sex. Presence of relevant medically attended episodes of asthma or chronic obstructive pulmonary disease (R91, R95, and R96), lung cancer (R84 and R85), myocardial infarction (K75), congestive heart failure (K77) or other cardiovascular disease (K74, K76, K78,

K79, K82, K83, and K84), chronic renal disease (U88 and U99), or immune-related disease (B73, B74, and B90) was documented. Prior health care use was recorded as the number of GP consultations, number of medications, referral to a specialist, and prior hospitalization for one of the possible complications in the 12 months preceding the epidemic. Furthermore, health insurance coverage was registered. In the Netherlands, this 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).

### Data analysis

A person was counted only once as a case for the first occurring hospitalization. Patients who were hospitalized and died afterward were counted once for the combined outcome measure and counted for both hospitalized cases and deaths. Bivariate comparisons for vaccinated and unvaccinated subjects were conducted using  $\chi^2$  test and Student's *t* test for categorical and continuous variables, respectively. In accordance with other reports (9,10,17), univariate and multivariable logistic regression models were used to obtain crude and adjusted odds ratios (ORs) (and their 95% CIs) of the association between vaccination and case status. The OR was used as an approximation of the relative risk. The adjusted vaccine effectiveness was calculated as  $(1 - \text{adjusted OR}) \times 100\%$  (11,21). The following potential confounders were added to the regression equation to adjust the vaccine effectiveness estimates: age, sex, health care insurance, presence of heart or lung disease, or other high-risk disease, as well as the number of medications and the number of GP visits during the 12 months before the start of the epidemic. The same approach was applied to obtain adjusted ORs in each of the relevant subgroups according to age (18–64 vs.  $\geq 65$  years) and first versus repeat vaccination. A two-sided *P* value  $< 0.05$  was considered to indicate statistical significance.

## RESULTS

### Baseline characteristics

In all, 192 case and 1,561 control subjects were included in the analysis. To gain more insights into differences between vaccinated and unvaccinated individuals, we recorded baseline characteristics

among the 1,561 control subjects. Overall, vaccinated control subjects were older, were more likely to have chronic heart or lung disease, and took a higher number of medication in the 12 months preceding the epidemic. Apart from health care insurance status, cases differed from control subjects for most characteristics (Table 2).

### Incidence of complications during the influenza epidemic

Among the 9,238 individuals with diabetes, 61 deaths (9 in the age-group 18–64 years and 52 in the elderly) and 131 hospitalizations (61 in the age-group 18–64 years and 70 in the elderly) occurred. To explore potential differences in incidence rates of outcomes between vaccinated and unvaccinated individuals during the 1999–2000 influenza A epidemic, we calculated the incidence rates per 1,000 person-periods in both groups using the figures of the total baseline cohort of 9,238 diabetic patients (Table 3). The incidence rate of any complication among the age-group 18–64 years was two times higher in unvaccinated (28.3 per 1,000) than in vaccinated (14.0 per 1,000) individuals. Among the elderly, incidence rates of hospitalization did not substantially differ between unvaccinated (11.2 per 1,000) and vaccinated (13.9 per 1,000) individuals. In this age-group, mortality rates were most noticeably different between the two groups.

### Vaccine effectiveness

In the age-group 18–64 years, hospitalizations for influenza, pneumonia, other acute respiratory disease, myocardial infarction, congestive heart failure, stroke, or diabetes event were prevented by 70% (95% CI 39–85; Table 4). Most hospitalizations were due to diabetes dysregulation (59 of 61 outcomes). Point estimate for the separate outcome hospitalization for diabetes dysregulation was slightly lower (60% [22–80]). The power of the study was inadequate to establish statistically significant difference in mortality rates in this younger age-group. Among individuals aged  $\geq 65$  years, vaccination prevented 56% (4–80%) of deaths after adjustments. In this age-group, hospitalization was prevented by 14% (–88 to 60), but this was not statistically significant. Among all individuals with diabetes, regardless of age, 56% (36–70) of any complication was prevented. Hospitalizations were prevented by 54% (26–71) and deaths by 58% (13–80). In first-vaccinated

Table 2—Baseline characteristics of case and control subjects in a study of the effectiveness of influenza vaccination in people with diabetes

Characteristic	Aged 18–64 years			Elderly aged ≥65 years			All adults aged ≥18 years		
	Case subjects	Control subjects	P value	Case subjects	Control subjects	P value	Case subjects	Control subjects	P value
n	70	369		122	1,192		192	1,561	
Vaccination	43 (61.4)	294 (79.7)	0.001	98 (80.3)	1,045 (87.7)	0.022	141 (73.4)	1,339 (85.8)	<0.001
Age (years)	53.1 ± 7.57	51.7 ± 10.0	0.257	76.7 ± 7.56	75.4 ± 6.69	0.045	68.1 ± 13.7	69.8 ± 12.6	0.081
Female sex	31 (44.3)	183 (49.6)	0.415	62 (50.8)	780 (65.4)	0.001	93 (48.4)	963 (61.7)	<0.001
NHI	51 (72.9)	265 (71.8)	0.859	101 (83.5)	921 (77.3)	0.121	152 (79.6)	1,186 (76.0)	0.275
Lung disease	13 (18.6)	45 (12.2)	0.149	37 (30.3)	191 (16.0)	<0.001	50 (26.0)	236 (15.1)	<0.001
Heart disease	12 (17.1)	52 (14.1)	0.507	65 (53.3)	493 (41.4)	0.011	77 (40.1)	545 (34.9)	0.156
Other disease*	2 (2.9)	4 (1.1)	0.241	7 (5.7)	28 (2.3)	0.027	9 (4.7)	32 (2.0)	0.022
GP visits†	1.54 ± 4.46	1.38 ± 2.84	0.696	4.49 ± 7.73	2.47 ± 3.53	<0.001	3.42 ± 6.86	2.21 ± 3.41	<0.001
Prescriptions†	1.67 ± 1.76	1.08 ± 1.39	0.002	3.26 ± 2.43	1.86 ± 2.20	<0.001	2.68 ± 2.34	1.67 ± 2.07	<0.001
Specialist care†	8 (11.4)	94 (25.5)	0.011	45 (36.9)	335 (28.1)	0.042	53 (27.6)	429 (27.5)	0.972
Hospitalization†	4 (5.7)	4 (1.1)	0.008	20 (16.4)	57 (4.8)	<0.001	24 (12.5)	61 (3.9)	<0.001

Data are means ± SD or n (%). P values compare case with control subjects. \*Other disease includes renal disease and immune-related disease; †no. in previous 12 months. NHI, National Health Insurance.

subjects, the primary end point was reduced by 47% (0.2–72), and in those who received vaccination in the year before, the reduction was 58% (4–81).

**CONCLUSIONS**— Our study clearly demonstrates substantial clinical benefits from influenza vaccination among adult individuals with diabetes, most with type 2, independent of age or prior vaccine uptake. However, some potential limitations need to be considered before accepting these results. Since immunization guidelines recommend vaccination for patients with high-risk conditions regardless of age (3), it is unethical to conduct a placebo-controlled trial (20,21). However, the nested case-control approach permits the assessment of vaccine effects, notably on infrequent severe end points such as hospitalization or death (17). Vaccination rates in control subjects were similar and comparable with estimates from other large Dutch cohorts (13,15,19). Further, the distribution of some important risk factors were not substantially different in vaccinated and unvaccinated control subjects and were similar to those observed in earlier studies (11,15). 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 informed about the vaccination status of their patients, we find it unlikely that this could have influenced the GPs diagnostic process and, by doing so, caused overestimation of actual vaccine effectiveness.

Because this study was performed in a Dutch routine-care setting, the GPs were not actively involved in recruiting patients and assessing the outcomes. When there was such a bias, we would expect a much higher reduction in the more specific end points, hospitalization for pneumonia or influenza, than in the less specific end points such as hospitalization for diabetes dysregulation. Obviously, the association of mortality and vaccination status cannot be influenced by such bias.

The outcome used in this study was hospitalization for influenza, pneumonia, other acute respiratory disease, myocardial infarction, congestive heart failure, stroke, or diabetes dysregulation or death from any cause. By far, most of the hospitalizations were due to diabetes dysregulation. The fact that, in proportion, diabetes events were most common is not surprising considering the fact that diabetic ketoacidosis is an important complication of influenza infection in patients with diabetes (22). We did not, however, perform virological analysis of our cases to confirm actual influenza infection.

Therefore, it is still possible that part of these hospitalizations were not actually caused by the influenza virus. The effect of such a misclassification bias, if anything, would be an underestimation of true vaccine effectiveness.

An important issue in clinical vaccine effectiveness studies is that, by definition, unselected vaccinated and unvaccinated patients tend to differ in their prognosis (20). In previous studies, it has been shown that risk factors such as higher age and presence of comorbidity are more common in vaccinated than unvaccinated individuals, which can influence observed associations (10,15). When we compare the death rate of 18.7 per 1,000 in the unvaccinated subjects aged ≥65 years in our study (Table 3) with the incidence rate of 6.7 per 1,000 in the original study (15), the clear indication is that in our study, all subjects are already at higher risk at baseline because they all have diabetes. This may also most probably have resulted in fewer differences in baseline characteristics between vaccinated and unvaccinated control subjects.

Table 3—Incidence rates of end points per 1,000 person-periods during the 1999–2000 influenza A epidemic

	Aged 18–64 years		Aged ≥65 years	
	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated
Deaths	3.1	2.0	18.7	8.4
Hospitalizations	25.2	12.0	11.2	13.9
Total	28.3	14.0	29.9	22.3

Incidence rates were calculated as the number of case-periods within an age subgroup divided by the number of individuals at baseline from the same group, multiplied by 1,000.

**Table 4—Influenza vaccine effectiveness in reducing morbidity and mortality during the 1999–2000 influenza A epidemic in individuals with diabetes**

Subgroups	Hospitalization	Death from any cause	Hospitalization or death
All adults aged $\geq 18$ years			
Vaccinated case subjects	98/131 (75)	43/61 (71)	141/192 (73)
Vaccinated control subjects	1,339/1,561 (86)	1,437/1,692 (85)	1,339/1,561 (86)
Unadjusted VE	51 (25–68)	60 (30–78)	54 (35–68)
Adjusted VE	54 (26–71)	58 (13–80)	56 (36–70)
Adjusted <i>P</i> value	0.002	0.019	<0.001
Aged 18–64 years			
Vaccinated case subjects	37/61 (61)	6/9 (67)	43/70 (61)
Vaccinated control subjects	294/369 (80)	331/430 (77)	294/369 (78)
Unadjusted VE	65 (36–80)	54 (–89 to 89)	63 (36–79)
Adjusted VE	70 (39–85)	24 (–706 to 93)	72 (46–85)
Adjusted <i>P</i> value	0.001	0.819	<0.001
Elderly aged $\geq 65$ years			
Vaccinated case subjects	61/70 (87)	37/52 (71)	98/122 (80)
Vaccinated control subjects	1,045/1,192 (88)	1,106/1,262 (88)	1,045/1,192 (88)
Unadjusted VE	0 (–107 to 51)	64 (32–81)	40 (2–63)
Adjusted VE	14 (–88 to 60)	56 (4–80)	39 (–5 to 65)
Adjusted <i>P</i> value	0.706	0.039	0.076

Data are *n* (%) or vaccine effectiveness (VE) (95% CI).

We only found more comorbidity in the vaccinated elderly, and this was solely with respect to chronic lung disease. In

the age-group 18–64 years, those vaccinated were not substantially different from unvaccinated subjects.

**Table 5—Results of adjustments for confounding using multivariable logistic regression analysis**

	Hospitalization or death	
	VE (95% CI)	<i>P</i> value
All adults aged $\geq 18$ years		
Unadjusted VE	54 (35–68)	<0.001
VE adjusted for age, sex, and NHI	51 (39–65)	<0.001
VE adjusted for the above plus mean GP visits, mean prescriptions, specialist care, and hospitalization	55 (34–69)	<0.001
VE adjusted for the above plus lung, heart, and other comorbid diseases	56 (36–70)	<0.001
Aged 18–64 years		
Unadjusted VE	63 (36–79)	0.001
VE adjusted for age, sex, and NHI	65 (38–80)	<0.001
VE adjusted for the above plus mean GP visits, mean prescriptions, specialist care, and hospitalization	72 (44–85)	<0.001
VE adjusted for the above plus lung, heart, and other comorbid diseases	72 (46–85)	<0.001
Elderly aged $\geq 65$ years		
Unadjusted VE	40 (2–63)	0.041
VE adjusted for age, sex, and NHI	35 (–6 to 61)	0.083
VE adjusted for the above plus mean GP visits, mean prescriptions, specialist care, and hospitalization	36 (–9 to 62)	0.105
VE adjusted for the above plus lung, heart, and other comorbid diseases	39 (–5 to 65)	0.076

NHI, National Health Insurance; VE, vaccine effectiveness.

We further minimized the possibility of “confounding by indication” by sampling into age subgroups and controlling for the confounding effect in the analyses. Furthermore, we had data on a number of other potentially confounding characteristics and adjusted for all of these by using logistic regression analysis (Table 5). However, we did not have information on some diabetes-specific factors, which may have confounded the association. Absence of confounding can only be guaranteed in adequately large randomized controlled trials, but it is very unlikely that the vaccine effectiveness estimates observed in this study, were influenced by residual confounding. If anything, observed estimations would be underestimations because vaccinated people in general are at higher risk for developing an end point.

Colquhoun et al. (10) observed a 79% reduction of hospitalizations in patients with diabetes of all ages, but in this study, 83% of case subjects were aged <65 years. The effectiveness estimate compares with the 70%, as observed among the 18- to 64-year age-group in our study. In an earlier study from the U.S., Hak et al. (11) found a 50% reduction in hospitalizations and death in elderly patients with diabetes in the first season in which the predominating influenza strains matched well with the vaccine. In the present study, with good matching of the vaccine, a vaccine effectiveness estimate of 39% (though not significant) compares with the U.S. study (11). Heymann et al. (12) did not find an additional benefit in patients with diabetes, but the study could be discussed because of the low influenza activity during the study season.

In our study, we only had information on the diagnosis of diabetes in general and could not distinguish between type 1 and type 2 diabetes. Since a decreased T-cell immune response has been found in type 1, but not type 2, diabetes (4) and most patients have type 2 diabetes (>90%), it remains unclear whether patients with type 1 diabetes can benefit from such vaccination. We also were unable to record ethnicity of all study subjects since such data are not routinely available in Dutch general practice. Data from the Dutch National Survey of General Practice also showed that only a minority of primary care patients is not of Dutch origin, making it difficult to draw conclusions about this specific group.

Regarding studies into annual revaccination, previous studies have reported

conflicting results. Hoskins et al. (23), who performed a trial of inactivated influenza vaccine in an English boarding school for boys, only observed significant protection in boys who were vaccinated for the first time, while Beyer et al. (24) did not observe differences in serological protection in those receiving the vaccine for the first time or repeatedly. Voordouw et al. (19), on the other hand, reported that annual influenza vaccination is associated with a reduction in all-cause mortality risk, particularly in older individuals in 2005, and first vaccination reduced mortality only marginally. In our study, we did not find a significant difference between those vaccinated for the first time and those who received a repeat vaccination.

In conclusion, the results of our study lend strong support to the view that patients with type 2 diabetes, like other high-risk individuals (15), benefit from annual influenza vaccination regardless of age, and efforts should be renewed to increase vaccination rates among this high-risk group. Results from a recent study (25) show that shortfall in the delivery of such routine preventive services is not only explained by patient characteristics but also by structure and revenue sources of physician practices. Influencing these factors might further increase vaccination rates among diabetes patients.

**Acknowledgments**—Funding for this study was provided by the Netherlands Health Care Insurance Board.

**References**

1. Muller LMAJ, Gorter KJ, Hak E, Goudzwaard WL, Schellevis FG, Hoepelman AIM, Rutten GEHM: Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. *Clin Infect Dis* 41:281–288, 2005
2. Smith SA, Poland GA: Use of influenza and pneumococcal vaccines in people with diabetes (Review). *Diabetes Care* 23: 95–108, 2000
3. American Diabetes Association: Influenza and pneumococcal immunization in diabetes. *Diabetes Care* 27 (Suppl. 1):S111–S113, 2004
4. Centers for Disease Control and Prevention: Estimated influenza vaccination coverage among adults and children: United

- States, September 1, 2004–January 31, 2005. *MMWR Morb Mortal Wkly Rep* 54: 304–307, 2005
5. Pozilli P, Zuccarini O, Lavicoli M, Andreani D, Sensi M, Spencer KM, Bottazzo GF, Beverely PC, Kyner JL, Cudworth AG: Monoclonal antibodies defined abnormalities of T-lymphocytes in type I (insulin dependent) diabetes. *Diabetes* 32:91–94, 1983
6. Pozilli P, Gale EAM, Visalli N, Baroni M, Crovari P, Frighi V, Cavallo MG, Andreani D: The immune response to influenza vaccination in diabetic patients. *Diabetologia* 29:850–854, 1986
7. Diepersloot RJA, Bouter KP, Van Beek R, Lucas CJ, Masurel N, Erkelens DW: Cytotoxic T-cell response to influenza A subunit vaccine in patients with type 1 diabetes mellitus. *Neth J Med* 35:68–75, 1989
8. McElhaney JE, Pinkoski MJ, Au D, Lechelt KE, Bleackley RC, Meneilly GS: Helper and cytotoxic T lymphocyte responses to influenza vaccination in healthy compared to diabetic elderly. *Vaccine* 14:539–544, 1996
9. Feery BJ, Hartman LJ, Hampson AW, Proietto J: Influenza immunization in adults with diabetes mellitus. *Diabetes Care* 6:475–478, 1983
10. Colquhoun AJ, Nicholson KG, Botha JL, Raymond NT: Effectiveness of influenza vaccine in reducing hospital admissions in people with diabetes. *Epidemiol Infect* 119:335–341, 1997
11. 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 3 large managed-care organizations. *Clin Infect Dis* 35: 370–377, 2002
12. Heymann AD, Shapiro Y, Chodick G, Shalev V, Kokia E, Kramer E, Shemer J: Reduced hospitalizations and death associated with influenza vaccination among patients with and without diabetes. *Diabetes care* 27:2581–2584, 2004
13. Hak E, Van Loon S, Buskens E, Van Essen GA, De Bakker D, Tacken MAJB, Van Hout B, Grobbee DE, Verheij TJM: Design of the Dutch Prevention of Influenza, Surveillance and Management (PRISMA) study. *Vaccine* 21:1719–1724, 2003
14. Hak E, Wei F, Grobbee DE, Nichol KL: A nested case-control study of influenza vaccination was a cost-effective alternative to a full cohort analysis. *J Clin Epidemiol* 57:875–880, 2004
15. Hak E, Buskens E, Van Essen GA, De Bakker DH, Grobbee DE, Tacken MAJB, Van

- Hout BA, Verheij TJM: Clinical effectiveness of influenza vaccination in persons younger than 65 years with high-risk medical conditions. *Arch Intern Med* 165: 274–280, 2005
16. Rimmelzwaan GF, De Jong JC, Bartelds AI, Dorigo-Zetsma JW, Fouchier RA, Osterhaus AD: Influenza season 1999/2000 and vaccine composition for the season 2000/2001. *Ned Tijdschr Geneesk* 144:1968–1971, 2000 [in Dutch]
17. Hak E, Hoes AW, Grobbee DE, Lammers JWJ, Van Essen GA, Van Loon AM, Verheij TJM: Conventional influenza vaccination is not associated with complications in working-age patients with asthma or chronic obstructive pulmonary disease. *Am J Epidemiol* 157:692–700, 2003
18. Nichol KL, Nordin J, Mullooly J, Lask R: Influence of advancing age on influenza vaccination among community dwelling elderly. *Int Congr Ser* 1263:98–100, 2004
19. Voordouw ACG, Sturkenboom MCJM, Dieleman JP, Stijnen T, Smith DJ, Van der Lei J, Stricker BHCH: Annual revaccination against influenza and mortality risk in community-dwelling elderly persons. *JAMA* 292:2089–2095, 2005
20. Hak E, Verheij TJM, Grobbee DE, Nichol KL, Hoes AW: Confounding by indication in non-experimental evaluation of vaccine effectiveness: the example of prevention of influenza complications (Review). *J Epidemiol Community Health* 56:951–955, 2002
21. Voordouw BCG, Van der Linden PD, Simonian S, Van der Lei J, Sturkenboom MCJM, Stricker BHC: Influenza vaccination in community-dwelling elderly: impact on mortality and influenza-associated morbidity. *Arch Intern Med* 163:1089–1094, 2003
22. Diepersloot RJA, Bouter KP, Hoekstra JBL: Influenza infection and diabetes mellitus: case for annual vaccination. *Diabetes Care* 13:876–882, 1990
23. Hoskins TW, Davies JR, Smith AJ, Miller LC, Allachin A: Assessment of inactivated influenza A vaccine after three outbreaks of influenza at Christ's Hospital. *Lancet* 1:33–35, 1979
24. Beyer WEP, Palache AM, Sprenger MJW, Hendriksen E, Tukker JJ, Darioli R, Van der Water GL, Masurel N, Osterhaus ADME: Effects of repeated annual influenza vaccination on vaccine sero-response in young and elderly adults. *Vaccine* 14:1331–1339, 1996
25. Pham HH, Schrag D, Hargraves JL, Bach PB: Delivery of preventive services to older adults by primary care physicians. *JAMA* 294:473–481, 2005

Downloaded from http://diabetesjournals.org/care/article-pdf/29/8/1771/593646/zdc00806001771.pdf by guest on 25 September 2023