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

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**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.

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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 decreased 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

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**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.

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**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 |
| McElhaney 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 ≥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 ≥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 ≥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 ≥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, local crepitations, bronchophony, temperature >38°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

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 ~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 − adjusted OR) × 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. ≥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 ≥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***

| | Aged 18–64 years | | | Elderly aged ≥65 years | | | All adults aged ≥18 years | | |
|---|---|---|---|---|---|---|---|---|---|
| Characteristic | 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 ≥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 *P* 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 *P* value | 0.001 | 0.819 | <0.001 |
| Elderly aged ≥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 *P* 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) | *P* value |
| All adults aged ≥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 ≥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.

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