Annual Revaccination Against Influenza and Mortality Risk in Community-Dwelling Elderly Persons

A. C. G. Voordouw, MD
M. C. J. M. Sturkenboom, PhD
J. P. Dieleman, PhD
Th. Stijnen, PhD
D. J. Smith, PhD
J. van der Lei, PhD
Bruno H. Ch. Stricker, MB, PhD

Context Although large-scale observational studies have demonstrated the effectiveness of influenza vaccination, no large studies have systematically addressed the clinical benefit of annual revaccinations.

Objective To investigate the effect of annual influenza revaccination on mortality in community-dwelling elderly persons.

Design, Setting, and Participants A population-based cohort study using the computerized Integrated Primary Care Information (IPCI) database in the Netherlands including community-dwelling individuals aged 65 years or older from 1996 through 2002. For each year, we computed the individual cumulative exposure to influenza vaccination since study start.

Main Outcome Measure Association between the number of consecutive influenza vaccinations and all-cause mortality vs no vaccination after adjusting for age, sex, chronic respiratory and cardiovascular disease, hypertension, diabetes mellitus, renal failure, and cancer.

Results The study population included 26071 individuals, of whom 3485 died during follow-up. Overall, a first vaccination was associated with a nonsignificant annual reduction of mortality risk of 10% (hazard ratio [HR], 0.90; 95% confidence interval [CI], 0.78-1.03) while revaccination was associated with a reduced mortality risk of 24% (HR, 0.76; 95% CI, 0.70-0.83). Compared with a first vaccination, revaccination was associated with a reduced annual mortality risk of 15% (HR, 0.85; 95% CI, 0.75-0.96). During the epidemic periods this reduction was 28% (HR, 0.72; 95% CI, 0.53-0.96). Similar estimates were obtained for persons with and without chronic comorbidity and those aged 70 years or older at baseline. Overall, influenza vaccination is estimated to prevent 1 death for every 302 vaccinees at a vaccination coverage that varied between 64% and 74%.

Conclusion Annual influenza vaccination is associated with a reduction in all-cause mortality risk in a population of community-dwelling elderly persons, particularly in older individuals.

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INFLUENZA-ASSOCIATED MORBIDITY and mortality increase with age, especially for individuals with high-risk conditions.[1,2] The estimated impact of annual influenza epidemics on morbidity and mortality on elderly persons and the effectiveness of influenza vaccination have been the basis for implementing nationwide influenza vaccination programs for elderly individuals.[3]

The effectiveness of vaccination has been reported to decrease in high-risk persons.[4-7] Annual influenza revaccination has been proposed as a strategy to increase vaccination effectiveness.[8-11] However, clinical studies have not always shown a consistent benefit of annual revaccination. In institutionalized elderly persons, annual revaccination resulted in improved survival,[12,13] whereas, in a placebo-controlled trial among 1838 community-dwelling elderly persons, prior vaccination did not further reduce the occurrence of clinical influenza.[4] In a trial of healthy adults (aged 30-60 years), annual influenza vaccination had no additional effect on the risk of clinically diagnosed influenzalike illness, although both first vaccination and repeat vaccination showed a greater decrease in virus shedding and better annual protection against influenza virus infection compared with placebo.[14,15] In a clinical trial among boarding school students, revaccination did not confer

See also Patient Page.

Author Affiliations: Pharmaco-epidemiology Unit, Departments of Internal Medicine and Epidemiology & Biostatistics (Drs Voordouw, Sturkenboom, Dieleman, Stijnen, and Stricker), Department of Medical Informatics (Drs Sturkenboom, Dieleman, and van der Lei), and Department of Virology (Dr Smith), Erasmus University Medical Center, Rotterdam, the Netherlands; Medicines Evaluation Board (Dr Voordouw) and Drug Safety Unit, Inspectorate for Health Care (Dr Stricker), the Hague, the Netherlands; and Department of Zoology, University of Cambridge, Cambridge, England (Dr Smith).
Corresponding Author: Bruno H. Ch. Stricker, MB, PhD, Department of Epidemiology & Biostatistics, Erasmus Medical Center, PO Box 1738, 3000 DR Rotterdam, the Netherlands (b.stricker@erasmusmc.nl).

any benefit with respect to serologically or virologically confirmed influenza.[16] A recent meta-analysis comparing single and multiple vaccinations showed that although 7 of 10 field trials supported sustained protection against laboratory-confirmed influenzalike illness upon revaccination, the pooled rate difference of 1.1% was not significant.[17]

Recommendations regarding annual vaccination are often based on the reported influenza-attributed mortality and morbidity and effectiveness of vaccination without systematic data on revaccination status.[18-21] So far, studies to establish the effectiveness of repeated influenza vaccinations within the scope of national programs have not been performed in a population-based setting.

Our objective was to investigate the relationship of influenza revaccination status on mortality in community-dwelling persons aged 65 years or older during the epidemic influenza seasons covering 1996-2002.

METHODS

Setting

In the Netherlands, a nationwide influenza vaccination program has been active since 1997. In the Dutch health care system, all persons are designated to their own general practitioner (GP) who files all relevant medical details on patients from primary care visits, hospital admissions, laboratory examinations, and visits to outpatient clinics. The vaccination program is executed by GPs during annual mass vaccination days in October and November, during which all individuals aged 65 years and older and adults and children with predefined risk factors are invited to participate in the vaccination campaign. General Practitioners register the vaccination date in the electronic patient record. Since 1994, the Integrated Primary Care Information (IPCI) Project at the Department of Medical Informatics of the Erasmus Medical Center in Rotterdam, the Netherlands, has assembled electronic patient records on a cumulative population of approximately 500 000 patients from approximately 150 GPs. The IPCI database is a general practice research database that contains information on all medical data, including demographic information, patient complaints and symptoms, diagnoses, results of laboratory tests, referral notes from consultants, and hospital admissions. The International Classification for Primary Care is used as the coding system for symptoms and diagnoses,[22] but these can also be included as free text. All prescriptions are recorded in the database, which includes drug name, Anatomical Therapeutical Chemical (ATC) code, dosage form, dose, prescribed quantity, and indication. The IPCI database is the sole repository of medical records, and no additional paper records of the patients are kept by the GPs. Patients and practice identifiers are altered to warrant anonymity. The system complies with European Commission guidelines on the use of data for medical research and has shown to be valid for pharmacoepidemiologic research.[6,23] The IPCI internal review board approved the project and patient consent was not required.

Study Population

In the IPCI database 49 818 individuals were 65 years or older at any time during the study period. First, we excluded all practices that did not consistently register influenza vaccination over the study years. Nonconsistent registration was defined as a difference between minimum and maximum annual vaccination coverage of at least 50% and/or a minimum vaccination coverage recording of less than 25%. After exclusion, 34 991 persons remained. In this remaining study population, we conducted a cohort study during the period between October 1, 1996, and September 30, 2002. We included patients who were 65 years or older on January 1 of the year of study start, who had a permanent status in 1 of the practices in the IPCI source population, and who had at least 1 year of recorded database history prior to study start to determine heath status and vaccination status. We excluded 8920 individuals who did not have a recorded database history in the GP practice of 1 year or more. The eligible population thus included 26 071 persons. Censoring was performed at death, moving out of the GP practice, or at the end of the study period, whichever came first.

Exposure Definition

The cumulative number of influenza vaccinations was determined between October 1 and December 31 of each calendar and was assigned to each individual on January 1 of the next year. This date was chosen to compensate for the slight variability in vaccination dates, mostly between late October and early December, and the lag time before vaccination becomes effective. (An additional analysis using actual date of vaccination did not substantively affect the results.) Exposure status was categorized into 9 mutually exclusive categories including nonexposed, first vaccination, second, third, fourth, fifth, and sixth (or seventh) vaccination, vaccination interruption, and restart. A first vaccination status was assigned to individuals who received the first vaccination after study entry with no recorded influenza vaccination prior to study entry. If persons were vaccinated prior to study entry they started with the number of previously recorded vaccinations. Upon each additional consecutive vaccination during the study period, the cumulative number of influenza vaccinations increased by one. When a vaccination series was interrupted, it was categorized as such. Finally, restart after 1 or more years of interruption was also categorized separately. Once in the interruption category, individuals remained in it until vaccination restart and vice versa. Consequently, in this time-varying approach of exposure analysis, individuals contributed information to different exposure categories during follow-up.

Outcome Definition

The primary outcome in this study was all-cause mortality. Death was identified from the demographic patient file and validated in the medical chart. Deaths occurring during the period January 1 and December 31 were allocated to the vaccination status defined in the period between October 1 and December 31 of the preceding year. In an

extra analysis, we compared mortality during the epidemic periods (defined as the first day of the first week of the recorded epidemic until the last days of the last week of the recorded epidemic) with a reference period during the summer months (July and August).

Covariates

Selection of covariates was based on an earlier study from our group in the same database.[6] In addition to age, sex, and epidemic year, we identified 6 disease clusters as potential confounders: chronic respiratory tract disease (chronic obstructive pulmonary disease, emphysema, chronic bronchitis, asthma); chronic cardiovascular disease (heart failure, angina pectoris, history of myocardial infarction or cerebrovascular accident, aortic aneurysm, chronic arterial dysfunction); hypertension; diabetes mellitus; chronic renal insufficiency; and malignancies. The presence of these conditions at study entry or their development at any time during follow-up was retrieved from the medical charts through automatic screening and further manual validation. Those who had no comorbidity at baseline and did not develop any of the predefined conditions during follow-up were considered as the population without comorbidity.

Information on the size of each influenza epidemic was obtained from Jan C. de Jong, PhD, of the National Influenza Center, Erasmus MC Rotterdam (written communication, August 21, 2003, and March 5, 2004).[24]

Analyses

To estimate the univariate association between vaccination, covariates, and death we used a Cox proportional hazards model. Multivariate time-varying Cox proportional hazard models were developed to estimate the hazard ratios (HRs) for different vaccination states while adjusting for all other risk factors.[25] In most analyses the nonexposed category was used as reference category. For the estimation of the HRs of revaccination vs first vaccination, the first vaccination was used as reference category. To fully adjust for the strong influence of age on death in this analysis, we used age in days as time axis. The exposure status of an individual on the date of death was compared with all individuals in the cohort on that moment during follow-up on which they had exactly the same age as the individual who died. We also adjusted for sex and for time since the beginning of the study to adjust for epidemic year. To adjust for comorbidity that occurred during follow-up, time-dependent covariates were used for the diseases defined above.

The association of vaccine exposure with mortality risk was evaluated in 3 analyses: any vaccination vs no previous vaccination; a first vaccination, revaccination, interruption, and restart vs no vaccination; and any revaccination vs a first vaccination. Subsequently, revaccination was further analyzed by second, third, fourth, fifth, and sixth or seventh vaccination.

Stratified analyses were conducted on the presence of comorbidity and age at study entry (65-69, 70-79, or >79 years).

All results were expressed as HRs with 95% confidence intervals (CIs). In the total population, numbers needed to vaccinate to save 1 death were calculated as: $1/[(1-e^{-\text{IRcontrol}\times\text{follow-up time}}]-[1-e^{-\text{IRindex}\times\text{follow-up time}}])$, where IR is the incidence rate. All analyses were performed using SAS software, version 8.2 using the procedure Proc Phreg. Statistical significance was set at $P\leq.05$.

RESULTS

Baseline characteristics of the population and univariate associations of covariates with all-cause mortality are provided in TABLE 1. Of the 26071 persons who were eligible for study entry, 3485

Table 1. Characteristics of the Study Population at Study Entry

Variable	No. (%) Population Characteristics at Study Entry (n = 26071)	No. (%) Deaths at Follow-up (n = 3485)	Risk of Dying During Follow-up, Univariate HR (95% CI)
Sex			
Women	10940 (42.0)	1667 (15.2)	1.27 (1.19-1.35)
Men	15131 (58.0)	1818 (12.0)	Reference
Age, y			
65-69	10490 (40.2)	537 (5.1)	Reference
70-74	5863 (22.5)	608 (10.7)	1.77 (1.73-1.81)
75-79	4669 (17.9)	747 (16.0)	
80-84	2761 (10.6)	686 (24.8)	
≥85	2288 (8.8)	907 (39.6)	
Year of study entry			
1996	10195 (39.1)	2089 (20.5)	Reference
1997	1325 (5.1)	142 (10.7)	0.66 (0.65-0.68)
1998	4667 (17.9)	493 (10.6)	
1999	7178 (27.5)	664 (9.3)	
2000	1528 (5.9)	70 (4.6)	
2001	1178 (4.5)	27 (2.3)	
Comorbidity			
None at study entry	12173 (46.7)	1034 (8.5)	Reference
Comorbidity at study entry*	13898 (53.3)	2451 (17.6)	2.15 (2.00-2.31)
Hypertension	6414 (24.6)	837 (13.0)	0.94 (0.87-1.01)
Diabetes mellitus	3000 (11.5)	583 (19.4)	1.59 (1.46-1.74)
Respiratory system	3487 (13.3)	689 (19.8)	1.69 (1.57-1.84)
Cardiovascular system	6099 (23.4)	1378 (22.6)	2.30 (2.15-2.46)
Cancer	1034 (4.0)	330 (31.9)	2.81 (2.50-3.15)
Renal dysfunction	221 (0.8)	87 (39.4)	3.41 (2.75-4.21)

Abbreviations: CI, confidence interval; HR, hazard ratio.
*During the follow-up period comorbidity developed in another 2903 individuals, resulting in a total of 16701 individuals with comorbidity at baseline or any time during follow-up.

died during follow-up. The mean duration of participation in the study was 3 years. The mean (SD) age at study entry was 73.1 (7.4) years and 58% were women. At baseline 53.3% of the population had some form of comorbidity, mostly hypertension (24.6%) and chronic cardiovascular diseases (23.4%). Mortality was strongly associated with age, sex, and comorbidity. The mortality rate was highest for individuals with chronic renal dysfunction or malignancies.

The vaccination coverage and vaccination status for each study year are shown in TABLE 2. During the total study period, the population studied received 62476 influenza vaccinations. Ninety-six percent of the vaccinations were given in October or November, and 3.6% in December. The annual vaccination coverage ranged from 64% in 1996 to 74% in 1999. A total of 5095 eligible individuals (19.5%) never received influenza vaccination during follow-up. Influenza epidemics during the study period were of mild to moderate severity (TABLE 3); the 2000-2001 season showed no clear epidemic activity. Generally, vaccine strains and the predominant circulating strain (mainly A[H3N2]) were well matched except for the 1997-1998 season.[24] The peak activity of influenzalike illness ranged between 7 cases per 10000 persons (2000-2001 season) and 32 cases per 10000 persons per week (1999-2000 season) and was observed between weeks 2 and 13.

In the total population, any vaccination was associated with a 22% lower risk of all-cause mortality (adjusted HR, 0.78; 95% CI, 0.72-0.85; TABLE 4). First vac-

Table 2. Vaccination Coverage and Vaccination Status per Influenza Epidemic Season

	1996-1997	1997-1998	1998-1999	1999-2000	2000-2001	2001-2002*
Eligible population						
Total	10195	10991	14302	19676	17234	16590
With comorbidity†	5445	6382	8532	11721	10571	10426
Total died	487	490	647	821	711	329
Vaccination coverage, No. (%)‡						
Not vaccinated	3655 (35.9)	3676 (33.4)	4608 (32.5)	5130 (26.1)	4567 (26.5)	4831 (29.1)
Vaccinated	6540 (64.1)	7315 (66.6)	9694 (67.5)	14546 (73.9)	12667 (73.5)	11759 (70.9)
With comorbidity	3906 (71.7)	4664 (73.1)	6245 (73.2)	9249 (78.9)	8218 (77.9)	7894 (75.7)
Vaccination status						
No vaccination	3655	2707	3130	4020	3114	2955
First	3030	1497	1061	849	824	395
Second§	3510	2661	3181	5477	1106	969
Third	. . .	3157	2390	2783	4361	996
Fourth	. . .	. . .	2832	2175	1667	3937
Fifth	. . .	. . .	. . .	2595	1588	930
Sixth or seventh	. . .	. . .	. . .	. . .	2123	3284
Interrupted	. . .	969	1523	1110	1453	1876
Restarted	. . .	. . .	185	667	998	1248

Abbreviation: Ellipses indicate no data.
*Follow-up in the 2001-2002 season ended in September.
†With comorbidity at baseline; a proportion of individuals developed comorbidity during follow-up (see Table 3).
‡Percentage in parentheses indicates the proportion of individuals with comorbidity being vaccinated.
§May also include multiple vaccinations of individuals who had only 1-year history available before study entry and who were vaccinated in that year. It is not known if they had any previous vaccinations.

Table 3. Epidemiological Characteristics of the Influenza Epidemic Seasons*

	Vaccine Strains			Predominant Epidemic	Antigenic	Epidemic Period, wk‡			Peak Influenzalike
Season	A(H3N2)	A(H1N1)	B	Strain(s)	Match†	Start	Peak	End	Illness§
1996-1997	Wuhan/353/95	Singapore/6/86	Beijing/184/93	A(H3N2)	+++	2	4	8	29
1997-1998	Wuhan/353/95	Bayern/7/95	Beijing/184/93	A(H3N2)	+	8	13	15	18
1998-1999	Sydney/5/97	Beying/262/95	Beijing/184/93	A(H3N2)	+++	6	8	11	22
1999-2000	Sydney/5/97	Beying/262/95	Beijing/184/93	A(H3N2)	+++	51	2	5	32
2000-2001	Moscow/10/99	New Caladonia/20/99	Beijing/184/93	B	+++	1	4	8	7
2001-2002	Moscow/10/99	New Caladonia/20/99	Sichuan/379/99	A(H3N2)	+++	2	9	12	13

*Information in this Table was provided by Jan D. De Jong, PhD.
†+ Indicates poor match (some cross-protection); ++, fair match (moderate cross-protection); +++, good match (substantial cross-protection); ++++, excellent match (identical strains or minimal differences).[21]
‡Influenzalike illness was defined as prodromal phase with feverishness plus at least 1 of the following symptoms: cough, coryza, sore throat, frontal headache, retrosternal pain, myalgia.
§Peak influenzalike illness denotes the maximum number of cases per week per 10 000 inhabitants in the Netherlands as reported by the general practitioners participating in the Continuous Morbidity Registration system of NIVEL (Netherlands Institute for Primary Health Care) during the peak of the epidemic.

cination was associated with a nonsignificant reduction in mortality risk of 10% in the total population (adjusted HR, 0.90; 95% CI, 0.78-1.03). Any revaccination was associated with a risk reduction of approximately 24% (adjusted HR, 0.76; 95% CI, 0.70-0.83), which was strongest during the epidemic period (adjusted HR, 0.72; 95% CI, 0.59-0.89) and was not significant during a reference summer period (July and August; adjusted HR, 0.89; 95% CI, 0.70-1.12). Compared with a first vaccination, revaccination was associated with a significantly reduced mortality risk of 15% (adjusted HR, 0.85; 95% CI, 0.75-0.96). During the epidemic period this risk reduction was 28% (HR, 0.72; 95% CI, 0.53-0.96). When each individual vaccination was modeled separately, the mortality risk showed a decreasing trend with additional consecutive vaccinations (FIGURE). Interruption of the vaccination series was associated with a strong and significant increase in mortality risk (adjusted HR, 1.25; 95% CI, 1.10-1.42). When the vaccination series was interrupted for more than 1 year, this risk estimate increased further, although it was no longer significant (adjusted HR, 1.83; 95% CI, 0.94-3.78). Restarting vaccination after an interruption resulted in a mortality risk reduction similar to that observed following revaccination. In the total population 1 death was prevented for every 302 vaccinations, or 1 for every 195 revaccinations.

Exclusion of the population with a history of vaccinations prior to study entry did not change the effect estimates (data available on request). Stratification for comorbidity showed that the largest effects following any vaccination and revaccination were observed in the subpopulation without comorbidity (Table 4). Revaccination was not associated with a reduction in mortality risk in persons aged 65 through 69 years at baseline (adjusted HR, 0.98; 95% CI, 0.78-1.23) but was significantly reduced in persons aged 70 through 79 years at baseline (adjusted HR, 0.78; 95% CI, 0.68-0.91), and persons aged 80 years and older at baseline (adjusted HR, 0.69; 95% CI, 0.61-0.78). This age-related difference following revaccination seemed to reflect age-related differences in causes of death. In the highest age groups, relatively more individuals died from causes that may be more likely to be influenced by influenza vaccination, such as infectious causes (HR following vaccination, 0.58; 95% CI, 0.43-0.79) or old age or "frailty" (HR following vaccination, 0.63; 95% CI, 0.55-0.73; TABLE 5).

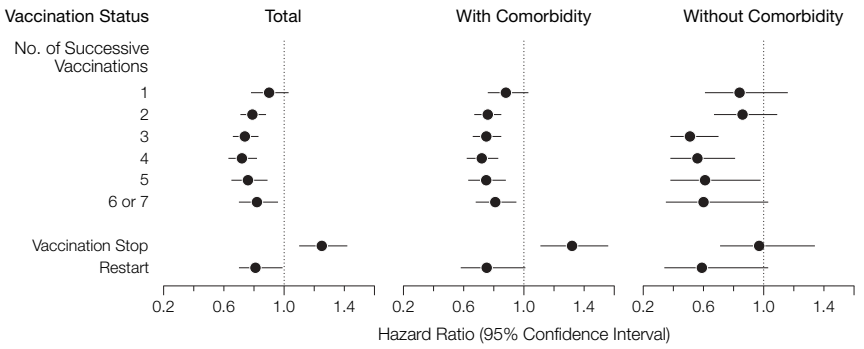
We assessed the possibility of confounding by indication, ie, the possibility that those who were not vaccinated were sicker than those who were. However, in our population, the proportion of the population with comor-

Table 4. Annual Adjusted Hazard Ratios of Death, Stratified by Comorbidity and Age

	Death, No. of Cases	Hazard Ratio (95% Confidence Interval)	
		Crude	Adjusted*
Total population			
Any vaccination	2225	0.91 (0.84-0.99)	0.78 (0.72-0.85)
First vaccination	284	0.97 (0.85-1.12)	0.90 (0.78-1.03)
Revaccination	1941	0.90 (0.83-0.98)	0.76 (0.70-0.83)
Vaccination interruption	366	1.43 (1.26-1.62)	1.25 (1.10-1.42)
Vaccination restart	121	0.91 (0.75-1.11)	0.81 (0.67-0.99)
Population without comorbidity†			
First vaccination	47	0.86 (0.62-1.18)	0.84 (0.60-1.16)
Revaccination	217	0.66 (0.54-0.80)	0.66 (0.54-0.80)
Population with comorbidity			
First vaccination	237	0.91 (0.78-1.06)	0.88 (0.76-1.03)
Revaccination	1724	0.82 (0.75-0.90)	0.75 (0.68-0.83)
Age at baseline, y			
65-69			
First vaccination	56	1.20 (0.87-1.66)	1.11 (0.81-1.53)
Revaccination	300	1.25 (1.00-1.56)	0.98 (0.78-1.23)
70-79 y			
First vaccination	109	1.02 (0.81-1.28)	0.93 (0.75-1.17)
Revaccination	803	0.95 (0.83-1.10)	0.78 (0.68-0.91)
≥80 y			
First vaccination	119	0.87 (0.70-1.07)	0.81 (0.66-1.00)
Revaccination	838	0.78 (0.69-0.88)	0.69 (0.61-0.78)

*Adjusted for comorbidity (respiratory tract disease, cardiac disease, hypertension, diabetes mellitus, renal dysfunction, and malignancy) and sex. Age adjustment by age in days as time axis.
†No recorded predefined comorbidity at baseline or developing at any time during follow-up.

Figure. Hazard Ratios for Mortality by Individual Vaccination States, Stratified by Population



Mortality risk is shown by the number of successive vaccinations, ie, first, second, third, fourth, fifth, more than 6, interruption of vaccination (stop), or restart. The hazard ratio indicates the mortality risk following vaccination vs no previous vaccination.

Table 5. Annual Adjusted Hazard Ratios of Cause-Specific Death

Cause of Death	No.	Age at Death, Mean (SD), y	Adjusted Hazard Ratio (95% Confidence Interval)*		
			Any Vaccination	First Vaccination	Revaccination
Overall	3485	81.5 (8.1)	0.78 (0.72-0.85)	0.90 (0.78-1.03)	0.76 (0.70-0.83)
Cardiovascular†	726	82.1 (7.9)	0.89 (0.73-1.08)	0.89 (0.65-1.23)	0.89 (0.73-1.08)
Chronic respiratory disease‡	180	80.1 (7.5)	1.13 (0.71-1.79)	1.30 (0.67-2.51)	1.11 (0.70-1.77)
Malignancies	549	77.8 (7.4)	0.87 (0.71-1.08)	0.96 (0.68-1.33)	0.85 (0.68-1.05)
Infections§	249	84.2 (7.5)	0.58 (0.43-0.79)	0.56 (0.31-1.00)	0.58 (0.43-0.79)
Diabetes mellitus	33	82.2 (8.9)	1.98 (0.60-6.58)	1.51 (0.25-9.14)	2.02 (0.60-6.76)
Renal insufficiency	34	80.0 (7.2)	1.23 (0.41-3.68)	2.25 (0.55-9.20)	1.11 (0.36-3.38)
"Natural death"‖	1087	83.8 (8.2)	0.63 (0.55-0.73)	0.83 (0.65-1.05)	0.61 (0.52-0.70)
Sudden death¶	458	79.2 (7.2)	0.82 (0.65-1.03)	1.05 (0.73-1.50)	0.79 (0.62-1.00)
Other causes#	169	79.8 (8.3)	1.11 (0.73-1.67)	1.02 (0.53-1.98)	1.12 (0.73-1.70)

*Adjusted for comorbidity (respiratory tract disease, cardiac disease, hypertension, diabetes mellitus, renal dysfunction, and malignancy) and sex. Age adjustment using age in days as time axis.
†Cerebrovascular accident, heart failure, cardiac asthma.
‡Emphysema, acute respiratory distress syndrome, exacerbation of chronic obstructive pulmonary disease, respiratory failure.
§Pneumonia, sepsis, septic shock, urosepsis.
‖Alzheimer disease, Parkinson disease, no specific diagnosis, decubitus, "natural death," old age with no other obvious reason.
¶Validated sudden cardiac death retrieved from other study in same patient population, found dead without preexisting cause.
#Euthanasia, "unnatural death," accident, postoperative death, preoperative death, dehydration, Creutzfeldt-Jakob disease, gastrointestinal bleeding, murder.

bid illnesses was 50.9% for those with no previous vaccination, 55.8% for those who refused (34% of all those who were not vaccinated), 68.9% for those who had an interruption, and 68.5% for those who had any vaccination in series, suggesting that those who were not vaccinated were at least as healthy as those who were. Furthermore, compared with nonusers who refused vaccination, the adjusted mortality risk following the first vaccination was an HR of 1.09 (95% CI, 0.93-1.28) and following revaccination, an HR of 0.93 (95% CI, 0.83-1.04). Compared with those who were not vaccinated and did not refuse, the adjusted HR for mortality following the first vaccination was 0.73 (95% CI, 0.63-0.85) and following any revaccination, 0.62 (95% CI, 0.56-0.70).

COMMENT

In this study, we showed that influenza vaccination is associated with a reduced risk of mortality in community dwelling elderly despite several mild epidemic seasons, and that revaccination is an effective strategy to further reduce or sustain reduced mortality risk in both healthy elderly individuals and in those with underlying chronic disease. In our population, annual revaccination was associated with a significant mortality reduction among those aged 70 years and older. This result may reflect differences in age-related causes of death, which probably were less influenced by vaccination in those at a younger age than those in the highest age groups. Additionally, the observed lack of effect in the youngest age categories may be a result of a lower baseline risk of death. Interruption of yearly influenza vaccination was associated with a significantly increased mortality, but after restarting vaccination, mortality risk reduced again to a revaccination status level. Absence of protection from the vaccination may be an explanation for the observed risk increase, since individuals who interrupted vaccination for 2 or more consecutive years had a further increase in mortality risk.

Although a protective association between mortality and revaccination status in elderly persons has been suggested previously, only 1 case-control study has examined this association. In this study, a previous vaccination significantly increased vaccine effectiveness in the next season.[9] However, the study was not population-based; approximately half of the individuals were institutionalized. Nichol et al[7,19] and Hak et al[5] studied the effect of influenza vaccination on long-term outcomes but did not take revaccination status into account. Gross et al[20] published a meta-analysis on mortality risk in 20 cohort studies. Based on the current study, the large variability in effects identified by Gross et al might be explained by different revaccination states, variations in epidemic activity, and population characteristics. It has also been proposed that variability of revaccination efficacy might be due to antigenic differences among the vaccine and epidemic strains.[26] Our study did not find an effect of first vaccination, but past studies and our previous study in the same database found a significant protective effect.[6]

Our study has several strengths. We were able to assess the overall annual and epidemic effectiveness of annual influenza vaccinations as well as the effect of individual revaccinations. The study was population-based and less subject to selection bias, information bias, and confounding. In the Dutch health care system, all individuals are designated their own GP, so selection bias is unlikely. Information bias may have occurred if the vaccination was not recorded. However, such misclassification would likely be random because exposure is prospectively recorded before death occurred. Such random misclassification would tend to reduce the size of the estimate, suggesting that the real protective effect could be even greater. All-cause mortality was chosen as an end point because it is an important outcome, which cannot be misclassified. Deaths were unlikely to have been missed since death rates in IPCI were similar to national data on mortality. As discussed above, confounding by indication is possible but in this study, comorbidity and a higher risk of mortality would be an indication for vaccination, reducing the likelihood of confounding as an explanation for the observed effect. Moreover, perceived good health has, among others, been reported as a reason for non-

compliance with the influenza vaccination program.[27] Indeed, compared with those refusing vaccination, mortality risk was not reduced following a first or revaccination. However, excluding those who refused vaccination from the reference category resulted in a significant adjusted risk reduction following a first and revaccination. In addition, we adjusted for chronic respiratory tract disease, cardiovascular disease, hypertension, diabetes mellitus, malignancies, and chronic renal insufficiency, either preexisting or having developed during follow up, because they were both indications for vaccination and independent risk factors for mortality. Even if some residual confounding by indication cannot be excluded, a poorer prognosis in individuals who were vaccinated would mean that our results would tend to underestimate the protective effect of annual revaccination.[25]

In summary, our study shows that annual revaccination against influenza in a population of community-dwelling elderly persons is associated with a reduction of mortality risk. This study supports the recommendation for yearly influenza vaccination for elderly individuals, not only for those with comorbid illness but also in those without comorbidity and in patients 80 years or older. Because influenza vaccination is inexpensive and safe, clinicians should recommend annual influenza revaccination for such patients.

Author Contributions: Drs Voordouw, Sturkenboom, Dieleman, van der Lei, and Stricker had full access to the IPCI database. All coauthors had full access to the data set for this study.
Study concept and design: Stricker, Voordouw, Sturkenboom, Dieleman.
Acquisition of data: Voordouw, van der Lei.
Analysis and interpretation of data: Stricker, Voordouw, Sturkenboom, Dieleman, Stijnen, Smith.
Drafting of the manuscript: Stricker, Voordouw, Sturkenboom, Dieleman.
Critical revision of the manuscript for important intellectual content: Stricker, Voordouw, Sturkenboom, Dieleman, Stijnen, Smith, van der Lei.
Statistical analysis: Stricker, Voordouw, Sturkenboom, Stijnen, Smith.
Obtained funding: Stricker.
Study supervision: Stricker, Sturkenboom, Dieleman, van der Lei.
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