Influenza Vaccination in Community-Dwelling Elderly

Impact on Mortality and Influenza-Associated Morbidity

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Background: Influenza-related morbidity and mortality have been extensively studied with hospital and reimbursement data. However, little is known about the effectiveness of the annual vaccination programs in generally healthy community-dwelling elderly. The objective of our study was to investigate the effectiveness of influenza vaccination in community-dwelling elderly during the 1996 to 1997 influenza epidemic.

Methods: We performed a population-based cohort study using the computerized Integrated Primary Care Information database in the Netherlands. Subjects who were 65 years and older in 1996 with a permanent status in a practice in the source population were considered eligible for study participation. Two cohorts were defined on the basis of vaccination status. We estimated and compared all-cause mortality, pneumonia, and clinical influenza infection rates between the cohorts.

Results: Influenza vaccination was associated with a significant reduction of morbidity and mortality in vaccinated elderly (relative risk [RR], 0.72; 95% confidence interval [CI], 0.60-0.87). Influenza infections decreased significantly in the vaccinated population (RR, 0.48; 95% CI, 0.26-0.91). Mortality was reduced significantly in elderly with comorbidity (RR, 0.67; 95% CI, 0.48-0.94). The risk reduction for pneumonia was non-significant (RR, 0.77; 95% CI, 0.55-1.07) but was temporally related to the peak influenza activity.

Conclusions: In this study, influenza vaccination was associated with decreased mortality and influenza infections in community-dwelling elderly. Our results indicate that, in a season of mild influenza activity and good antigenic match between vaccine strains and circulating strains, influenza vaccination reduced mortality in the vaccinated population. Our data support an annual vaccination strategy for all community-dwelling elderly.

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considered representative of vaccine effectiveness assessment in that particular season or the target population defined by the influenza vaccination programs. For clinical protection in defined target populations, the antigenic match between vaccine strain(s) and circulating strain(s), vaccination coverage, annual revaccination, demographic characteristics, health status, and possible attack rate of the population of interest are at least as important as immune responsiveness.

The influenza season of 1996 to 1997 was of mild severity, with a good match between vaccine strain and the predominant circulating strain (A/H3N2/Nanchang/933/95). A peak activity of influenza-like illness of 28.8/10,000 persons was observed in week 4 of 1997, with a distribution in elderly similar to that of the general population. The objective of the present study was to investigate the effectiveness of influenza vaccination in community-dwelling elderly who were 65 years or older during this influenza season.

METHODS

SETTING

Since 1992, the Integrated Primary Care Information (IPCI) Project at the Department of Medical Informatics of the Erasmus Medical Centre in Rotterdam, the Netherlands, monitors a population of approximately 485,000 patients. The IPCI Project gathers all medical data from 125 general practitioner (GP) practices, 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, but these can also be included as free text. In the database, all prescriptions are recorded and include drug name, anatomical therapeutical chemical code, dosage form, dose, prescribed quantity, and indication. Repeat prescriptions are also recorded. As the system is fully automated, no paper records are held concurrently. Patient and practice identifiers are omitted to ensure anonymity. The system complies with European guidelines on the use of data for medical research and has been shown to be valid for pharmacoepidemiologic research.

DESIGN AND EXPOSURE DEFINITION

To assess the effectiveness of influenza vaccination, we conducted a retrospective cohort study. Persons who were 65 years or older in 1996 with a permanent status in one of the practices in the IPCI source population, and who had visited the GP at least once during the study period, were considered eligible for study participation. The study period ran from September 1, 1996, until June 1, 1997, including a 3-month enrollment period and a fixed period of 6 months of follow-up. For every individual who had received an influenza vaccination, 1 age- and sex-matched unvaccinated control subject was randomly selected. To facilitate age matching, the complete eligible population was split into 5-year categories (65-69, 70-74, 75-79, 80-84, and ≥85 years). The index date was defined as the date of vaccine administration and was thus the start of follow-up. Data on influenza vaccination were gathered from the prescription file (anatomical therapeutical chemical code J07BB) and from free-text notifications in individual patient records. Matched controls had the same index date as their vaccinated counterparts.
enza vaccination (42.5% of the eligible population). From the remaining 8911 nonvaccinated elderly, we selected age- and sex-matched controls. Baseline characteristics of these patients are given in Table 1. Because of the matching procedure, the mean age for the vaccinated (vaccine cohort) and nonvaccinated (control cohort) groups was almost identical. The vaccine and control groups, however, differed significantly in baseline prevalence of underlying diseases. Chronic respiratory diseases, including emphysema and chronic obstructive pulmonary disease, were 77% more frequent in the vaccine cohort. Heart failure and angina pectoris were, respectively, 49% and 31% more frequently noted. Malignancies were 24% more prevalent in the vaccine cohort. The prevalences of diabetes mellitus and hypertension in the vaccine cohort were, respectively, 51% and 11% higher. A greater than 2-fold higher prevalence of renal dysfunction was seen, albeit at a low background incidence. Overall, the prevalence of any serious comorbidity was 25% higher in the vaccine than in the control cohort. There was no substantial difference between the vaccine and control cohorts in duration of the comorbidity. In the vaccine cohort, 3 times as many individuals had been vaccinated against influenza in the preceding year.

Table 2 gives the relative risks of the outcomes of interest in the index and control cohorts. In the total population, vaccination was associated with a significantly lower incidence of pooled events (death, pneumonia, or influenza), all-cause mortality, and influenza infections, after adjustment for respiratory tract disease, cardiovascular, malignant, or miscellaneous diseases; history pertains to the earliest notification of one or more of these diseases in the automated patient profile.
In the subpopulation with comorbidity, 1 death was prevented in approximately every 170 vaccinated individuals. In the subpopulation with comorbidity, vaccination was associated with a significant risk reduction of death but not pneumonia. The reduced risk of influenza infection in this subpopulation was nonsignificant.

In the absence of comorbidity, relative risks adjusted for revaccination status showed a risk reduction for the pooled events and for pneumonia. For the total population, the risk reduction for pneumonia was visualized in a life table as the time to event (Figure). Risk reduction became prominent approximately 2 months after vaccination (ie, the first weeks of 1997, the time of peak influenza activity). Finally, effect modification by age and sex is shown in Table 3. Only in the age category 65 to 74 years was vaccination associated with a significant reduction of all events, and effectiveness decreased with increasing age; in addition, men seemed to benefit more than women from influenza vaccination.

COMMENT

In our study, influenza vaccination effectively prevented mortality and morbidity in elderly under everyday circumstances in a season with a good match between vaccine strain(s) and circulating strain(s). Although in individuals with comorbidity, influenza vaccination failed to show a protective effect against pneumonia, mortality was significantly reduced. It is known that most of the excess mortality caused by influenza and/or pneumonia is attributed to elderly with high-risk conditions. Possibility, elderly with an impaired clinical condition die as a result of influenza before developing pneumonia, or pneumonia is not recognized because symptoms in the elderly may be less prominent. Our data suggest that the effectiveness of influenza vaccination declines with age. This has also been shown in a randomized, placebo-controlled trial in healthy elderly followed up in one GP practice. As in our study, that trial showed a risk reduction of approximately 50% in clinical influenza in healthy elderly. Observational cohort studies mostly address influenza-related hospital admissions or focus on elderly in institutions or with high-risk conditions. In a recent large-scale cohort study in community-dwelling elderly, a significant risk reduction of hospital admission–associated mortality was observed. Limitations of that study, however, were that outpatient mortality and morbidity were not in-

### Table 2. Crude and Adjusted Relative Risks of Death, Pneumonia, or Influenza After Influenza Vaccination*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Vaccine Cohort</th>
<th>Control Cohort</th>
<th>Preventive Fraction‡</th>
<th>Crude RR (95% CI)</th>
<th>Adjusted RR (95% CI)§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Rate†</td>
<td>No.</td>
<td>Rate†</td>
<td></td>
</tr>
<tr>
<td>Total population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any event]</td>
<td>226</td>
<td>5.3</td>
<td>275</td>
<td>6.5</td>
<td>0.226</td>
</tr>
<tr>
<td>Death</td>
<td>143</td>
<td>3.3</td>
<td>164</td>
<td>3.8</td>
<td>0.132</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>72</td>
<td>1.6</td>
<td>83</td>
<td>1.9</td>
<td>0.158</td>
</tr>
<tr>
<td>Influenza</td>
<td>16</td>
<td>0.4</td>
<td>32</td>
<td>0.7</td>
<td>0.429</td>
</tr>
<tr>
<td>With comorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any event]</td>
<td>122</td>
<td>7.2</td>
<td>115</td>
<td>8.3</td>
<td>0.133</td>
</tr>
<tr>
<td>Death</td>
<td>75</td>
<td>4.3</td>
<td>77</td>
<td>5.5</td>
<td>0.214</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>44</td>
<td>2.5</td>
<td>29</td>
<td>2.1</td>
<td>-0.190</td>
</tr>
<tr>
<td>Influenza</td>
<td>5</td>
<td>0.3</td>
<td>10</td>
<td>0.7</td>
<td>0.571</td>
</tr>
<tr>
<td>Without comorbidity</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any event]</td>
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<td>4.1</td>
<td>160</td>
<td>5.6</td>
<td>0.268</td>
</tr>
<tr>
<td>Death</td>
<td>68</td>
<td>2.6</td>
<td>88</td>
<td>3.0</td>
<td>0.133</td>
</tr>
<tr>
<td>Pneumonia</td>
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<td>1.1</td>
<td>54</td>
<td>1.8</td>
<td>0.389</td>
</tr>
<tr>
<td>Influenza</td>
<td>11</td>
<td>0.4</td>
<td>22</td>
<td>0.7</td>
<td>0.429</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.
*Boldface type indicates a significant difference between groups.
†Incidence rate expressed as number of cases per 100 patient-years.
‡Preventive fraction calculated as (IR_{control} − IR_{vaccine})/IR_{control}, where IR indicates incidence rate.
§In the total population and the subpopulation with comorbidity: adjusted for respiratory tract disease, cardiac disease, hypertension, diabetes mellitus, renal dysfunction, and vaccination history.
¶Any event was defined as either death or pneumonia or influenza, whichever came first.
¶¶In the population without comorbidity; adjusted only for vaccination history.

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Annual influenza vaccination has been proposed as a strategy to increase effectiveness. In institutionalized elderly, annual revaccination as well as vaccination coverage was shown to be the most consistent contributors to survival. This is supported by evidence from a meta-analysis; however, the evidence has been questioned. Also in our study, preliminary assessment of annual revaccination appeared to enhance survival, although numbers were too small in the different subpopulations to allow for appropriate conclusions.

Epidemiologic studies under everyday circumstances may suffer from selection bias, information bias, and confounding. As GPs play a central role in the Dutch health care system and cover the complete population, selection bias was highly unlikely. Also, information bias was unlikely, since influenza vaccination was recorded by computer, the vaccination is supplied almost exclusively by GPs in the Netherlands, and the primary outcome “mortality” is difficult to misclassify. Misclassification of pneumonia is probably modest; all cases were confirmed radiologically and/or microbiologically. However, it is possible that influenza was underestimated in the vaccine cohort because physicians were aware of the vaccination status of their patients. A potential problem was confounding by indication. Although the national recommendation was to vaccinate those who were 65 years and older, generally healthy individuals do not always follow such advice. In our study, confounding by indication was likely, since preexisting respiratory or cardiovascular tract disease were independent risk factors for increased mortality, as was a history of influenza vaccination. These factors were thus adjusted for. As we may not be aware of all comorbidity, residual confounding cannot be excluded. However, this probably means that our estimates are conservative and that true protection may be higher.

In conclusion, our results indicate that, in a season of mild influenza activity and good antigenic match between vaccine strain(s) and circulating strain(s), influenza vaccination reduces influenza-related morbidity and all-cause mortality in community-dwelling elderly. The decrease in mortality was most prominent in elderly with high-risk conditions. Vaccine efficacy, calculated as a risk reduction in mortality of 33% in this subpopulation, could be translated to approximately 170 vaccinated individuals to prevent 1 death. Hence, our data suggest that a national policy to vaccinate all those who are 65 years and older against influenza can be successful. We argue that the assessment of the benefits of annual influenza vaccination programs should focus on survival and primary and secondary influenza-related morbidity in community-dwelling elderly. Such data may improve the cost-effectiveness estimates of influenza vaccination programs, where health care resource use includes GP visits and drug use in addition to hospitalizations.

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### REFERENCES


