

Do recommended high-risk adults benefit from a first influenza vaccination?

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Abstract

It is unknown whether a first influenza vaccination protects high-risk adults from severe morbidity and mortality during influenza epidemics. As part of the PRISMA nested case–control study, we aimed to evaluate the effectiveness of first-time and repeat influenza vaccinations in adult persons recommended for vaccination aged between 18 and 64 years during the 1999–2000 influenza A epidemic. After adjustments, 69% of hospitalizations for acute respiratory or cardiovascular disease or death were prevented in first-time vaccinees (95% percent confidence interval [95% CI]: 8–90%). The corresponding figure in persons who were vaccinated before was 85% (95% CI: 36–96%). Adult persons with high-risk medical conditions can substantially benefit from a first and repeat influenza vaccination prior to an epidemic.

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1. Introduction

Voordouw et al. recently showed that among elderly persons a first influenza vaccination reduced the risk of mortality during the influenza season only marginally, notably in those below 70 years of age [1]. This might influence vaccine uptake in elderly persons vaccinated for the first time in which induction of antibodies through first vaccinations might be sub optimal. However, this finding may not necessarily be applicable to younger persons who have special difficulties to comply with vaccination recommendations [2]. A meta-analysis of influenza vaccine trials among healthy younger persons showed no differences in serological protection rates between persons who received first or repeat vaccinations [3]. Furthermore, it remains to be established whether the occurrence of acute cardio-respiratory disease requiring hospital care during influenza epidemics

can be influenced by a first vaccination. We therefore carried out secondary data analysis of the Dutch Prevention of Influenza, Surveillance and Management (PRISMA) nested case–control study, which primarily aimed to establish the effectiveness of influenza vaccination in preventing clinical outcomes in influenza seasons with epidemic activity [4,5]. In this report we assessed the risk of hospitalization and mortality during the 1999–2000 influenza A(H3N1) epidemic after first and repeat influenza vaccination in adult persons recommended for vaccination under 65 years of age [4].

2. Methods

2.1. Study design and population

Design and results of the PRISMA study have been extensively described elsewhere [4–6]. In short, we conducted the case–control study in a cohort of patients of any age eligible for annual influenza vaccination according to Dutch primary care immunization guidelines prior to the study season. Recommended groups for influenza vaccination included persons

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aged 65 years and older, and younger persons with a high-risk medical condition including chronic bronchitis, emphysema, asthma, and other respiratory diseases; acute or chronic ischemic heart diseases, heart failure, atrial fibrillation, and other heart disease; cerebrovascular disease, diabetes mellitus, chronic renal disease, chronic staphylococcal infection, immune-related diseases, and patients in nursing homes and homes for the elderly. Healthy children aged 6–24 months, pregnant women and health care workers in general were not recommended for vaccination. Persons with known anaphylactic hypersensitivity to eggs or its components have a contra-indication for vaccination and medical records were scrutinized to exclude such patients. During the study season, 91 practices with 75,227 study patients were included. Of this study cohort, 33% of subjects were high-risk adults aged 18 to 64 years ($n = 24,928$) and for the purpose of this study we analyzed data on cases and controls from this sub-cohort.

During the 1999–2000 influenza A(H3N2) epidemic, with good matching of the vaccine with circulating strains, incident cases were defined as a person-period of hospitalization because of influenza (International Classification of Primary Care [ICPC] code [R80], pneumonia [R81]), other acute respiratory diseases (acute bronchitis [R78], (exacerbation of) chronic bronchitis [R91], (exacerbation of) emphysema [R95], (exacerbation of) asthma [R96]), acute otitis media [H71], myocardial infarction [K75], congestive heart failure [K77] or stroke [K90], or death from any cause. For the potential cases that had a general practitioner (GP) referral to hospital that was labeled as an exacerbation of the asthma/COPD, we scrutinized all medical records to see whether a prescription for oral corticosteroids was given. These additional eligibility criteria were developed to ascertain acute onset of the chronic diseases. For each possible case identified by a computerized search on ICPC-codes in April–May after the study season, four control persons without an endpoint were randomly selected by computer from the remainder of that season's base-line cohort. Sampling of controls was conducted within the same age-subgroup as the case and during the same season.

2.2. Endpoints and statistical analysis

The primary endpoint was a composite of hospital admission for acute respiratory or cardiovascular disease, or death from any cause, and secondary endpoints were the separate components hospitalization or death. Cases could experience a hospital admission or could die from any cause. Those cases that subsequently experienced both outcomes were counted as a person-period for both separate endpoints and as a first person-period for the combined endpoint. We derived estimates of vaccine effectiveness in reducing these endpoints for persons who received the influenza vaccination for the first time and for those who received the vaccine also in the season prior to the 1999–2000 influenza season (1998). We further adjusted effect estimates for potential confounders including age, gender, health care insurance status, history of respi-

ratory and cardiac disease, diabetes, renal or other disease, medication use, prior primary care visits or hospitalizations, and specialist care using multivariate logistic regression analysis. Estimates of vaccine effectiveness (VE) and their 95% confidence intervals (95% CI) were given in percentage as (1-odds ratio \times 100%).

3. Results

In all, the primary composite endpoint occurred in 64 persons with 70 person-periods of hospitalization or death. Among the cases, non-fatal hospitalizations occurred in 17 cases (four pneumonia, six exacerbations of chronic pulmonary disease, two congestive heart failure, four myocardial infarction and one stroke), and 41 persons died in the community without prior hospitalization. In six persons, hospitalizations resulted in a fatal outcome (one pneumonia, four exacerbations of chronic pulmonary disease and one myocardial infarction). Influenza vaccine uptake was more than twice as high in controls who received the vaccine before (94%) than among those who received it for the first time (44%). Vaccinated subjects (both first and repeat vaccinated persons) were older and showed a higher prevalence of some high-risk diseases than unvaccinated subjects (Table 1). Also, they were more often insured through the National Health Insurance (NHI), indicating a lower social economic status. Moreover, these subjects received more hospital care. Characteristics of persons who received the vaccine for the first time were not much different from those who received the vaccine repeat times, except for specialist care in the previous 12 months.

After adjustments, a first influenza vaccination was associated with substantial reductions in the primary and secondary endpoints (Table 2). Point estimate of vaccine effectiveness estimates were not substantially different from the cohort of persons who received repeat vaccinations and differences were statistically non-significant (p -value for interaction > 0.05).

4. Discussion

These data on a younger age-cohort complement those from Voordouw et al. [1] and showed that in contrast to their findings among elderly persons, first vaccinations in younger high-risk adults were associated with significant benefits. Although our study lacked statistical power to make conclusions about benefits regarding hospitalizations with repeat vaccinations in high-risk younger adults, the point estimates showed substantial reductions. Importantly, the risk of mortality was substantially lower among high-risk adults who received repeat vaccinations.

To appreciate these findings some issues need to be considered. The used case-control approach enables the assessments of the effects of vaccination on infrequent severe endpoints such as hospitalization or death [4]. The distribution

Table 1
Base-line characteristics estimated from controls for the group of high-risk adults

| Characteristic | Unvaccinated <i>N</i> = 532 | First vaccination <i>N</i> = 379 | <i>p</i> -value* | Repeat vaccinations <i>N</i> = 867 | <i>p</i> -value** |
|--|-----------------------------|----------------------------------|------------------|------------------------------------|-------------------|
| Mean age (S.D.) | 42 (14) | 49 (12) | <0.001 | 48 (14) | <0.001 |
| Male sex | 254 (48) | 170 (45) | 0.392 | 399 (46) | 0.532 |
| NHI | 339 (64) | 266 (70) | 0.041 | 612 (71) | 0.008 |
| Asthma/COPD | 288 (54) | 174 (46) | 0.014 | 406 (47) | 0.007 |
| Heart disease | 74 (18) | 88 (23) | 0.039 | 211 (24) | 0.003 |
| Diabetes mellitus | 57 (11) | 68 (18) | 0.002 | 180 (21) | <0.001 |
| Other disease ^a | 121 (23) | 75 (20) | 0.285 | 161 (19) | 0.059 |
| Mean no. of GP visits ^b | 0.3 (1.3) | 0.4 (1.4) | 0.753 | 0.7 (2) | 0.001 |
| Mean no. of prescriptions ^b | 0.5 (1.0) | 0.4 (1.0) | 0.085 | 0.8 (1.3) | <0.001 |
| Specialist care ^b | 41 (8) | 26 (7) | 0.634 | 140 (16) | <0.001 |
| Hospitalization ^b | 5 (1) | 9 (2) | 0.083 | 17 (2) | 0.134 |

NHI: National Health Insurance; GP: general practitioner.

^a Other disease: renal disease, immune-related disease.

^b In previous 12 months.

* *p*-value comparing persons who received vaccine for the first time with unvaccinated persons.

** *p*-value comparing persons who received vaccine for the second time or more with unvaccinated persons.

Table 2
Effect of first and repeat influenza vaccination (VE in %) in reducing hospitalization and mortality among adult high-risk persons 18–65 years of age during the 1999–2000 influenza A epidemic

| Subgroups | Composite endpoint | Hospitalization for ARD or CVD | Death from any cause |
|---|--------------------|--------------------------------|----------------------|
| First vaccination in high-risk persons 18–64 years | | | |
| No. vaccinated cases/total no. cases (%) | 9/31 (29) | 1/8 (13) | 8/27 (30) |
| No. vaccinated controls/total no. controls (%) | 379/853 (44) | 379/853 (44) | 379/853 (44) |
| Unadjusted vaccine effectiveness (95% CI) | 49 (–13; 77) | 82 (–46; 98) | 47 (–22; 77) |
| Adjusted vaccine effectiveness (95% CI) | 69 (8; 90) | 97 (13; 99) | 65 (–10; 89) |
| Adjusted <i>p</i> -value | 0.036 | 0.040 | 0.073 |
| Repeat vaccination in high-risk persons 18–64 years | | | |
| No. vaccinated cases/total no. cases (%) | 26/33 (79) | 13/15 (87) | 14/20 (70) |
| No. vaccinated controls/total no. controls (%) | 867/925 (94) | 867/925 (94) | 867/925 (94) |
| Unadjusted vaccine effectiveness (95% CI) | 75 (40; 90) | 56 (–97; 93) | 84 (58; 94) |
| Adjusted vaccine effectiveness (95% CI) | 85 (36; 96) | 71 (–330; 97) | 92 (48; 99) |
| Adjusted <i>p</i> -value | 0.010 | 0.370 | 0.008 |
| Statistical interaction first vs. repeat vaccinations in high-risk persons 18–64 years (<i>p</i> -value) | 0.433 | 0.306 | 0.132 |

Abbreviations: ARD—influenza, pneumonia, acute bronchitis, exacerbation of chronic pulmonary disease; CVD—acute myocardial infarction, congestive heart failure; high-risk: with chronic medical conditions with an indication for influenza vaccination (see Section 2).

of some important characteristics in vaccinated and unvaccinated controls was similar to figures observed in earlier vaccination studies and not substantially different between persons who received the vaccine for the first time or multiple times. Furthermore, the potential for recall bias was minimized through the complete review of prospectively collected data in routine medical care from computerized medical records.

A major issue in non-experimental evaluation of vaccines is that by definition, patients are selected by their general practitioner or by themselves to be vaccinated which may lead to confounding bias [7]. As also shown by Voordouw et al.'s study [1], the presence of risk factors is higher among vaccinated than unvaccinated persons which may have influenced observed associations. However, we minimized this so-called 'confounding by indication' in both the design and data-analysis phases of the study [7]. First, we only admitted patients with current indications for vaccination as

verified by the GP into the study cohort. Second, since age and presence of high-risk disease are major confounders, we frequency-matched cases and controls on these factors by sampling in subgroups and controlled for their confounding effect in the analyses. Third, we had information on many additional potential confounders and adjusted for these using logistic regression analysis. Obviously, only a large enough randomized controlled trial will fully guarantee absence of confounding, but it is very unlikely that the observed vaccine effectiveness estimates are materially influenced by residual confounding. If so, the reported estimations can only be valued as underestimations since in general vaccinated persons run a higher risk for developing an endpoint than unvaccinated persons as shown in Table 1.

The number of mean GP visits and medical drug prescriptions were rather low. There may be two explanations for this: first, about 8% of the patient population is under treatment by a specialist and therefore visits and medications in primary

care are limited for these persons. Second, the high-risk diseases (mostly asthma) in many adult patients in primary care have a rather mild course that either does not need chronic treatment or regular GP visits.

Finally, we had information on exposure to influenza vaccination for only two influenza seasons and therefore could not analyze potential differences for those persons who interrupted vaccinations. In Beyer's study, such an effect was also not studied and it remains to be established whether such an interruption influences the effects of vaccination. Obviously, the vaccine can only be protective against severe and infrequent clinical outcomes when influenza activity is high and the vaccine matches the seasonal viral strains [8]. More studies are needed to determine the long-term effectiveness and cost-effectiveness of such a vaccination program.

Among the main determinants of compliance with vaccine recommendations is the perception of benefit from the vaccine and health care workers should not miss the opportunity to educate younger high-risk patients about the significant benefits of vaccination.

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