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

Voorouw 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...
aged 65 years and older, and younger persons with a high-
risk medical condition including chronic bronchitis, emphy-
sema, asthma, and other respiratory diseases; acute or chronic
ischemic heart diseases, heart failure, atrial fibrillation, and
other heart disease; cerebrovascular disease, diabetes melli-
tus, 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 ana-
phylactic 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, inci-
dent 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 [R06]), acute otitis media
[R71], myocardial infarction [K75], congestive heart fail-
ure [K77] or stroke [K90], or death from any cause. For the
potential cases that had a general practitioner (GP) refer-
rnal 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 ascer-
tain 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 with-
out 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 ad-
mission 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 esti-
mates 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-
atory and cardiac disease, diabetes, renal or other disease,
médication use, prior primary care visits or hospitalizations,
and specialist care using multivariate logistic regression anal-
ysis. Estimates of vaccine effectiveness (VE) and their 95%
confidence intervals (95% CI) were given in percentage as
(1-odds ratio × 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 pul-
monary disease, two congestive heart failure, four myocardial
infarction and one stroke), and 41 persons died in the com-
munity without prior hospitalization. In six persons, hospi-
talizations resulted in a fatal outcome (one pneumonia, four
exacerbations of chronic pulmonary disease and one myocar-
dial 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 asso-
ciated with substantial reductions in the primary and sec-
ondary endpoints (Table 2). Point estimate of vaccine effec-
tiveness estimates were not substantially different from the
cohort of persons who received repeat vaccinations and dif-
fereces were statistically non-significant (p-value for inter-
action > 0.05).

4. Discussion

These data on a younger age-cohort complement those
from Vooroulw 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 conclu-
sions about benefits regarding hospitalizations with repeat
vaccinations in high-risk younger adults, the point estimates
showed substantial reductions. Importantly, the risk of mor-
tality was substantially lower among high-risk adults who
received repeat vaccinations.

To appreciate these findings some issues need to be con-
sidered. The used case-control approach enables the assess-
ments of the effects of vaccination on infrequent severe end-
points such as hospitalization or death [4]. The distribution
### Table 1

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

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

* NHI: National Health Insurance; GP: general practitioner.
  
  a Other disease: renal disease, immune-related disease.
  
  b In previous 12 months.

### 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

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Composite endpoint</th>
<th>Hospitalization for ARD or CVD</th>
<th>Death from any cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>First vaccination in high-risk persons 18–64 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. vaccinated cases/total no. cases (%)</td>
<td>9/31 (29)</td>
<td>1/8 (13)</td>
<td>8/27 (98)</td>
</tr>
<tr>
<td>No. vaccinated controls/total no. controls (%)</td>
<td>379/853 (44)</td>
<td>379/853 (44)</td>
<td>379/853 (44)</td>
</tr>
<tr>
<td>Unadjusted vaccine effectiveness (95% CI)</td>
<td>49 (−13; 77)</td>
<td>82 (−46; 98)</td>
<td>47 (−22; 77)</td>
</tr>
<tr>
<td>Adjusted vaccine effectiveness (95% CI)</td>
<td>69 (48; 90)</td>
<td>97 (−39; 79)</td>
<td>65 (−10; 89)</td>
</tr>
<tr>
<td>Adjusted p-value</td>
<td>0.036</td>
<td>0.040</td>
<td>0.073</td>
</tr>
<tr>
<td>Repeat vaccination in high-risk persons 18–64 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. vaccinated cases/total no. cases (%)</td>
<td>26/33 (79)</td>
<td>13/15 (67)</td>
<td>14/20 (70)</td>
</tr>
<tr>
<td>No. vaccinated controls/total no. controls (%)</td>
<td>867/925 (94)</td>
<td>867/925 (94)</td>
<td>867/925 (94)</td>
</tr>
<tr>
<td>Unadjusted vaccine effectiveness (95% CI)</td>
<td>75 (−15; 65)</td>
<td>56 (−57; 70)</td>
<td>64 (−58; 58)</td>
</tr>
<tr>
<td>Adjusted vaccine effectiveness (95% CI)</td>
<td>85 (36; 96)</td>
<td>71 (−33; 97)</td>
<td>92 (48; 99)</td>
</tr>
<tr>
<td>Adjusted p-value</td>
<td>0.010</td>
<td>0.370</td>
<td>0.008</td>
</tr>
<tr>
<td>Statistical interaction first vs. repeat vaccinations in high-risk persons 18–64 years (p-value)</td>
<td>0.433</td>
<td>0.306</td>
<td>0.132</td>
</tr>
</tbody>
</table>

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 reduced.
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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Conflict of interest: None declared.

References