Comparison of two vaccination programmes in preventing influenza-related hospitalization among the elderly during two consecutive seasons

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Abstract
The protective effect of influenza vaccine against influenza related hospitalization is well established at an individual level, but the effect of vaccination programme at the population level is unknown. In this study we compared a risk disease-based free-of-charge influenza vaccination programme in preventing hospitalizations due to influenza or pneumonia and cardiovascular diseases during 2 consecutive influenza seasons 1992/93 and 1993/94 in 43 municipalities in northern Finland. Vaccinations were carried out and reported by local staff in health centres. Data of hospital treatment periods were obtained from the National Hospital Discharge Register. During the influenza seasons the number of hospitalizations due to cardiovascular diseases and influenza/pneumonia increased by 13%. In the 1993/1994 season the increase in the study area with the risk disease-based vaccination programme was 22 per 1000 persons (95% CI 19–24), and with an age-based programme 3.3 per 1000 persons (95% CI 2.5–4.0), while the increase in the 1992/1993 season in both areas was 3–4 per 1000. The excess of hospitalization related to influenza epidemics is mostly due to cardiovascular diseases and varies from year to year, as do the benefits gained by vaccination.

Introduction
The benefits of influenza vaccination in preventing hospitalization and death among elderly people have been demonstrated in several studies during 2 decades in the USA and Canada [1–5], and also in Europe [6,7]. National recommendations on influenza vaccination vary a great deal. The 2 main variables in influenza vaccination strategies are whether the vaccine is recommended to all persons over a certain age, or only to those with predefined risk diseases, and how completely the vaccine is reimbursed [8]. Generally, higher levels of vaccine use have been found to be associated with specific reimbursement programmes [9]. Regardless of the vaccination strategy, the acceptance of influenza vaccine usually remains substantially below 100% coverage [9,10]. In Finland, the influenza vaccination strategy has been a topic of discussion for some years. The 2 alternatives have been whether to continue the current risk disease-based free-of-charge influenza vaccination policy or to widen it to all persons aged 65 y and above. The aim of this study was to obtain data that would aid in the decision. The unique feature of our study is that the comparison was made between vaccination programmes at the population level, rather than between vaccinated and non-vaccinated individuals, as has been the design in all previous studies.

In this study we used as outcome measures, hospitalization due to influenza or pneumonia and due to cardiovascular diseases. We considered it important to include also hospitalizations due to cardiovascular diseases among the outcome measures, because previous studies indicate that only
one-third of the excess mortality during an influenza outbreak can be accounted for by influenza or pneumonia diagnoses [11,12]. Thus, focusing on reduction of hospitalization or deaths due to those 2 diseases only would lead to an underestimated benefits of influenza vaccine, which in turn would have a negative impact on its use.

This study is 1 arm of the Pneumococcal and Influenza Vaccination Research (PIR) project. Previous publications related to this study have analysed factors associated with vaccination coverage [13,14] and the incremental effectiveness of pneumococcal vaccination over influenza vaccination [15].

Patients and methods
The strategy of this study was to compare at the population level the protective effect of 2 vaccination programmes carried out in 2 adjacent geographically defined areas during 2 consecutive influenza seasons. All persons who were 65 y of age or above and who lived in those areas were included in the study, whether they had accepted the vaccination or not. The protocol of the Pneumococcal and Influenza Vaccination Research (PIR) project was approved by the ethical committee of Oulu University Hospital.

The influenza vaccination programmes under comparison were a risk disease-based vaccination programme and an age-based vaccination programme. The risk disease-based programme has been a part of the Finnish vaccination programme since 1980; this has meant vaccination free of charge at the local health centre for all persons belonging to a number of predefined medical risk groups. The risk conditions have been centrally defined by the National Board of Health or the Ministry of Social Affairs and Health. Each health centre has received a number of doses estimated to cover the risk groups. The centres could request further supplies, but the total number of doses procured for the country has at times limited the availability of the vaccine. Persons not belonging to any of the risk groups could have purchased the vaccine from a pharmacy, but a physician’s prescription was needed, and there was no reimbursement. When calculating the coverage of the vaccinations, both the free-of-charge and self-paid vaccinations administered by the health centres were included. In the new age-based vaccination programme in this study, influenza vaccine was offered free of charge to all persons aged 65 y and above. Those born in an odd y were also offered pneumococcal polysaccharide vaccine in addition to the influenza vaccine, as described elsewhere [15]. Since the study revealed no differences in the incidence of pneumonia suggestive of a protective effect of the pneumococcal vaccine, we here treat the data as a single cohort irrespective of the pneumococcal vaccine.

In 1992 all municipalities (n = 66) in the county of Oulu and in the southern part of the county of Lapland in northern Finland were requested to participate in the study. 55 municipalities of the 66 decided to participate; the local Board of Health Services made the decision. The 55 municipalities were then divided into 3 programme areas matched by geographical location. Cities were allocated separately so that the urbanization rate was as equal as possible in each area. The municipalities were not allowed to choose their vaccination programme. At the time of the start of the study, newspapers and local radio disseminated general information about influenza as a disease and influenza vaccination, but no personal letters were sent to the target population.

The risk disease-based area consisted of 14 municipalities (number of persons aged 65 y or above, 16,288). In the age-based area, there were 29 municipalities and 20,638 persons aged 65 y or above. In the third area (12 municipalities, 22,864 persons aged 65 y or above), the vaccination programme was changed from risk disease-based in 1992 to age-based in 1993; this area was not included in the present study in order to keep the design as simple as possible.

The outcome measures were the excess of hospitalization during influenza seasons due to influenza or pneumonia (diagnoses 480–485, 4870A) and cardiovascular diseases (390–459), International Classification of Disease 9th revision) compared to the corresponding baseline hospitalization data (see below). The data of hospitalization events were obtained from the register kept by the National Research and Development Centre for Welfare and Health. The register includes all patients treated in hospitals in Finland. It contains information on both the main and additional diagnoses as well as the date of hospitalization and discharge. Virological surveillance data collected from Finland in the WHO National Influenza Centre at KTL were retrospectively used to define the time periods of influenza outbreaks in the present study. The first influenza period from 8 February to 18 April 1993 (70 d) covered 87% of the laboratory-confirmed infections with influenza in the KTL surveillance material during the 1992/1993 epidemic season (461 influenza B and 106 influenza A; the percentages of patients aged 65 y or above were 6% and 14%, respectively) (Table I). The second influenza period was defined from 15 November 1993 to 31 January 1994 (78 d). It covered 92% of the confirmed cases during the 1993/1994 epidemic season (491 influenza A and 7 influenza B); 11% of infections
with influenza A concerned patients aged 65 y or above).

Corresponding ‘inter-epidemic’ periods of time in the previous y when no or little influenza was recorded in the Finnish community served as baselines for the calculation of the excess hospitalization. During the first of these, from 8 February to 18 April 1992, the outbreak of the 1991/92 season was tapering off but still 98 (18%) of the total number of 551 laboratory-confirmed cases of influenza A were recorded. Fortunately, in 1992/93 only sporadic cases of influenza B were detected, and the following season was to be caused mainly by influenza B [16]. During the second inter-epidemic period from 15 November 1992 to 31 January 1993, a new outbreak was just starting, and the corresponding rate was 1.3% (9/713).

The vaccine was administered at the local health centres by their regular staff as their routine annual influenza vaccination task. The self-paid vaccines were administered in a similar manner. Contraindications were hypersensibility to any component of the vaccines or acute febrile illness. Terminally ill persons were not actively offered the vaccines. The health centres reported all vaccinations with a special report form to the study office.

The influenza vaccine used in autumn 1992 was the trivalent 1992/C193 Vaxigrip manufactured by Pasteur Merieux Serums & Vaccins containing the strains A/Beijing 353/89 (H3N2), A/Singapore 6/86 (H1N1) and B/Yamagata 16/88. In autumn 1993, 2 influenza vaccines were used: the trivalent split-virion influenza Vaxigrip manufactured by Pasteur-Merieux Serums & Vaccins containing the strains A/Beijing 32/92 (H3N2), A/Texas 6/86 (H1N1), and B/Panama 45/90, and trivalent surface antigen vaccine Influvac manufactured by Solvay Duphar B.V. in the Netherlands containing the strains A/Beijing 32/92 (H3N2), A/Taiwan 1/86 (H1N1), and B/Panama 45/90. The pneumococcal vaccine given to the participants was 23-valent pneumococcal polysaccharide vaccine PNEUMO 23, manufactured by Pasteur Mérieux Serums & Vaccins.

The excess of hospitalization was expressed both as the excess numbers of events and as relative increases. The 95% confidence intervals were calculated using Confidence Interval Analysis software [17].

### Results

Vaccination coverage among persons aged 65 y or above in the municipalities implementing the risk disease-based programme was 19% in 1992 and 20% in 1993 (the range between municipalities was 14 to 27%, and 11 to 28%). In the municipalities implementing the age-based programme the corresponding figures were 48% (38 to 69%), and 49% (39 to 87%). The reasons for the large variation between municipalities have been discussed in a separate report [13].

During the baseline periods of altogether 148 d, a total of 4449 hospitalizations (30 per d) due to influenza, pneumonia or cardiovascular diseases were recorded (Table II). Influenza or pneumonia accounted for 358 of these hospitalizations, and cardiovascular diseases for 4091 events.

### Table I. The observation periods, epidemic viruses, epidemic activities and match of vaccine.

<table>
<thead>
<tr>
<th>Influenza season</th>
<th>Time of observation</th>
<th>Virus* (Number of laboratory identifications)</th>
<th>activity*</th>
<th>Match of vaccineb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992/1993</td>
<td>Feb 8 to April 18 1993</td>
<td>A (H3N2) (106), B (461)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>1993/1994</td>
<td>Nov 15 1993 to Jan 31 1994</td>
<td>A (H3N2) (491), B (7)</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

*aBased on the analysis of respiratory tract infections among Finnish recruits [16].

bFrom low (+) to high (+++); interpretation based on antigenic and genetic analysis published previously [19,21].
vaccination area, the number of hospitalizations in the influenza season 1993/1994 (when most of the excess hospitalizations occurred) increased by 350 events (22 per 1000 persons, 95% CI 19-24), while the increase in the area with age-based vaccination programme was only 67 events (3.3 per 1000, 95% CI 2.5-4.0) The corresponding figures for the 1992/1993 season were an excess of 3 per 1000 in the risk disease-based programme area, and 4.4 per 1000 persons in the age-based programme area.

Discussion

We conducted a prospective influenza and pneumococcal vaccination study in the elderly population during 2 consecutive influenza seasons. In contrast to previous studies, the intervention evaluated was a public health measure, a vaccination programme of one kind or another, and thus all individuals whether vaccinated or not, living in the area of the programme in question were included in the study. As expected, the vaccination coverage reached was higher, at 50%, in the age-based programme area than in the risk disease-based area, at 20%.

During the first influenza season observed, only a modest, statistically non-significant, excess of hospitalizations (4%) due to influenza/pneumonia or cardiovascular diseases was recorded, while the excess was greater (11%) during the second season and showed a large difference between the programme areas: 3% in the age-based area and 21 in the risk disease-based area. The results are in concordance with the virological data from the surveillance [18-20]. During the season 1992/1993 less active B virus was predominant and the match of vaccine virus with epidemic virus was only modest. The areas did not differ significantly from each other, and the influenza epidemic was associated with a small, non-significant number of excess hospitalizations in each area. The next epidemic was caused by the more active H3N2 subtype influenza A virus. Simultaneously the match of vaccine was excellent [16,18,21]. The excess of hospitalization rate was higher than in the previous season, and different in the 2 programme areas depending on the vaccination programme used. The data from this period also show the importance of cardiovascular diseases as an influenza-related disease burden. Although the relative risk for excess hospitalization due to influenza or pneumonia was higher than that due to cardiovascular diseases (1.7 vs 1.3), the number of patients needing hospital treatment was 4.5 times higher for cardiovascular diseases due to the 10-fold higher incidence of cardiovascular diseases compared to influenza or pneumonia.

However, there are several factors which weaken the conclusion of an association between the vaccination programmes and the hospitalization rate. This was an ecological study, in which measurements were carried out at a group level. The results cannot be applied as an effectiveness study of influenza vaccine at an individual level. The data were obtained from 3 different sources: vaccination

<table>
<thead>
<tr>
<th>Cardiovascular diseases</th>
<th>Influenza or pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First season</strong></td>
<td><strong>Second season</strong></td>
</tr>
<tr>
<td>( n ) Per 1000 (95% CI)</td>
<td>( n ) Per 1000 (95% CI)</td>
</tr>
<tr>
<td>Risk disease-based programme</td>
<td>24</td>
</tr>
<tr>
<td>Age-based programme</td>
<td>58</td>
</tr>
</tbody>
</table>

Table II. The base-line rates of hospitalizations due to influenza or pneumonia and due to cardiovascular diseases; the hospitalizations during the comparison periods per 1000 persons aged 65 y or above.

Table III. Excess of hospitalization for cardiovascular disease and for influenza or pneumonia in the first influenza season (8 February to 18 April 1993), and the second season (15 November 1993 to 31 January 1994), over the baseline rate in the comparison periods (the same dates in 1992 and 1992/1993).
register of the study group, national hospital discharge register, and influenza surveillance register kept by the influenza centre in KTL. The vaccination register included only those vaccines given by the public health service, which underestimates the vaccination coverage in the risk disease-based areas. The relatively low interest of the elderly population for influenza vaccination demonstrated by the low participation rate in the free-of-charge programme gave us reason to believe that the error caused was rather small. The data from the vaccination register define the vaccination status of the population only at the time of vaccination. The effect of migration and mortality on the vaccination status during the time of survey is unknown. There were no predefined criteria for the endpoint diseases. That can explain the differences in the hospitalization rates between the areas during the non-influenza seasons. It is also possible that the diagnostic criteria for outcome diseases may have varied during the study. Although the vaccination status of patients was not recorded in patient files, clinicians working in the hospitals of the study area were aware of the vaccination programme in the surrounding municipalities, but we consider a bias unlikely because of this general knowledge.

The influenza seasons were defined by using the data at the national level. There was no influenza surveillance in the municipalities attending the study. The exact period of time of circulating influenza in the study area is unknown. Thus, it is possible that in relation to the circulating influenza, the areas were not comparable with each other during the fixed surveillance periods. The definition of an influenza period is problematic. The beginning is usually sharp, but sporadic cases can be found for a long period of time at the end of the season. This gives the researchers a possibility to define the season so that the results support the study hypothesis. This could be prevented by blinding a person who defines the season from the occurrence of the outcome measures; however, in this study there was no such blinding.

The marked difference between the populations in the areas of the 2 vaccination programmes was the average of the vaccination coverage, 50% in the municipalities with the age-based programme and 20% (or slightly more because of self-paid vaccines administered in the private sector) in municipalities with the risk disease-based programme. Two comments are relevant: first, the coverage rates are low in both cases considering the 20% coverage in the risk disease-based area compared with the 33% of the target population receiving reimbursed medication for the diseases in question [22]. The low interest in influenza vaccination seems typical of this age group, and the reasons for it are varied [13,23]. Secondly, the difference in the vaccination coverage between the areas was relatively small. Could it be responsible for the difference in excess hospitalization during the influenza seasons found in this study? We believe so. Previous reports suggest that influenza may react strongly in either direction to changes in the vaccination status of the population. In a study by Carman et al., vaccinating half of health care workers led to a substantial decrease in the mortality of patients in a long-term care unit [24]. In Japan, stopping the mandatory influenza vaccination of school children has led to increased influenza mortality among elderly people [25].

Our results clearly speak for the vaccination programme that yields highest vaccination coverage. Benefits of influenza vaccination vary from y to y, as shown also in several previous studies [26–28] depending on the activity of influenza virus, and the antigenic match between vaccine and epidemic virus. Both are factors that cannot be predicted at the time when decision about vaccination is to be made. Influenza vaccination can be considered as an insurance, the benefits of which will become reality when an accident takes place.

References


