Risk of invasive pneumococcal infections among working age adults with asthma

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ABSTRACT

Background Information about the risk of invasive pneumococcal infection (IPI) among adults with asthma is limited and inconsistent. To evaluate this association, a population-based case—control study was conducted.

Methods Cases of IPI (Streptococcus pneumoniae isolated from blood or cerebrospinal fluid) were identified through national, population-based laboratory surveillance during 1995—2002. To maximise exclusion of chronic obstructive pulmonary disease, the analysis was limited to patients aged 18—49 years and 10 selected age-, sex- and health district-matched controls for each case from the Population Information System. Information on underlying medical conditions was obtained through linking surveillance data to other national health registries. Asthma requiring ≥1 hospitalisation in the past 12 months was defined as high risk asthma (HRA); low risk asthma (LRA) was defined as entitlement to prescription drug benefits and no hospitalisation for asthma in the past 12 months.

Results 1282 patients with IPI and 12,785 control subjects were identified. Overall, 7.1% of cases and 2.5% of controls had asthma (6.0% and 2.4% had LRA whereas 1.1% and 0.1% had HRA, respectively. After adjustment for other independent risk factors in a conditional logistic regression model, IPI was associated with both LRA (matched OR (mOR) 2.8; 95% CI 2.1 to 3.6) and HRA (mOR, 12.3; 95% CI 5.4 to 28.0). The adjusted population-attributable risk was 0.039 (95% CI 0.023 to 0.055) for LRA and 0.01 (95% CI 0.0035 to 0.017) for HRA.

Conclusions Working age adults with asthma are at increased risk of IPI. In this population, ~5% of disease burden could be attributed to asthma. These findings support adding medicated asthma in adults to the list of indications for pneumococcal vaccination.

Streptococcus pneumoniae is a leading cause of serious illness, particularly among those with certain underlying medical conditions. Chronic obstructive pulmonary diseases (COPDs) are established risk factors for invasive pneumococcal infection (IPI), but there has been uncertainty as to whether persons with asthma without prolonged oral corticosteroid use are at increased risk and if they should be vaccinated with pneumococcal polysaccharide vaccine (PPV23). Available information regarding asthma and risk of IPI is limited and somewhat inconsistent. To evaluate the association between asthma and IPI among adults aged 18—49 years, we conducted a nationwide, registry- and population-based case—control study.

METHODS

Surveillance

In Finland (population, 5.2 million) all clinical microbiology laboratories, including private laboratories, notify (generally electronically) all bacterial isolations from blood and cerebrospinal fluid (CSF), including S pneumoniae to the National Infectious Disease Registry (NIDR) which is maintained by the National Institute of Health and Welfare (THL). Each of these mandatory notifications includes information on the causative microbe, date and type of specimen, date of birth, sex and the patient’s place of treatment (healthcare facility).

Ascertainment of cases and controls

A case of IPI was defined as an illness in which S pneumoniae was isolated from blood and/or CSF from 1 January 1995 to 31 December 2002. Among the overall 4611 episodes of IPI for whom National Identity Codes were available at the primary diagnostic laboratory, 4357 (94.5%) first episodes of disease were identified. The 1222 (29.4%) patients who were aged 18—49 years were included in the case—control study. As the differential diagnosis of asthma and COPD in older adults is difficult, we restricted our study population to persons aged 18—49 years to maximise exclusion of COPD and to reduce confounding from cigarette smoking-related lung disease.

For each patient, 10 controls matched on age (year of birth ±1 year), sex and health district of residence were randomly selected from the National Population Information System.

Definitions and identification of underlying medical conditions

Information on underlying medical conditions for patients and controls was obtained by linking the case—control study database to four national, population-based healthcare registries by using each individual’s unique National Identity Code. These databases included the National Social Insurance Institution (NSII), the National Hospital Discharge Register (HILMO), the Cancer Registry and the NIDR. The patient’s date of the first positive culture for S pneumoniae was used as the reference date for cases and their respective controls.

Definitions of asthma and exclusion of COPD

Patients and controls with asthma were defined as persons who had been granted a prescription drug benefit for asthma or COPD by the NSII, or who had a record of hospitalisation for these conditions during 12 months before the reference date in the HILMO database. High risk asthma (HRA) (International Classification of Diseases, 9th and 10th Revision (ICD-9, ICD-10) codes in appendix 1) was
defined as a record in the HILMO of at least one hospitalisation with an ICD-coded primary diagnosis for asthma in the past 12 months. Persons with low risk asthma (LRA) were defined as those entitled to NSII prescription drug benefit and no hospitalisation for asthma during the 12 months before the reference date. Overall, 80 (84.2%) of 95 patients and 308 (98.1%) of 314 controls had a record of prescription drug benefit available in the NSII database; the rest were identified through hospital admission data. Only 4 (0.5%) patients and none of controls had a record of hospitalisation for COPD in the past 12 months; these cases were excluded from the multivariable analysis.

The NSII uses standard criteria for determining the patient’s eligibility for prescription drug benefit. For asthma and COPD, the criteria include a physician’s certificate verifying the diagnosis and determining the severity of illness (using lung function tests, including spirometry, and need for prescription medications for at least 6 months (appendix 2)). Although asthma is not distinguished from COPD in the NSII database because both conditions are assigned the same reimbursement group code, we considered our study population to consist of individuals with medicated asthma because of restriction to persons <50 years of age.2 Therefore, in the Results and Discussion sections the cases and controls with a prescription drug benefit are referred as having ‘asthma’.

Other medical conditions
The presence of the following underlying medical conditions among patients and controls was defined as an NSII record indicating a prescription drug benefit for these conditions: diabetes mellitus, congenital or acquired immunodeficiency, rheumatic and other autoimmune diseases requiring immunosuppressive treatment, solid organ and bone marrow transplantation, cardiac failure and renal failure. Alcohol-related diseases, chronic liver diseases, diseases of the spleen and CSF leak were defined as records in the HILMO with one or more ICD-coded discharge diagnoses within 12 months before the reference date (appendix 1). Diagnosis of haematological malignant neoplasm within 5 years before the reference date and non-haematological malignancies within 1 year was obtained from the Cancer Registry, and infection with HIV from the NIDR.

Serotyping of bacterial isolates
*S. pneumoniae* isolates sent to the reference laboratory at the KTL as a part of national surveillance from 1995 to 2002 were serotyped as described previously.4 Pneumococcal serotypes were grouped as follows: 7-valent pneumococcal conjugate vaccine (PCV7) serotypes (4, 6B, 9V, 14, 18C, 19F and 23F); 10-valent (adding serotypes 1, 5 and 7F); 13-valent (adding serotypes 3, 6A and 19A); PPV23 serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F); and all other serotypes/groups.

Statistical analysis
For calculating the average annualised incidence of IPI among persons with asthma, the total number of persons 18–49 years of age who had prescription drug benefits for asthma or COPD during 1995–2002 in the NSII database was used as the denominator. To identify independent factors associated with IPI and to control for confounding, we developed a conditional logistic regression model. Asthma was the main variable of interest; covariates included other underlying conditions for which PPV23 is recommended.1 Matched ORs (mORs) and 95% CIs were calculated to compare risk factor characteristics between patients and controls. Adjusted population-attributable risks (PARs) for the independent risk factors in the model were calculated as described previously.5 PAR estimates the public health impact of a particular exposure—that is, the proportion of disease that could be prevented if the exposure was eliminated, expressed as a percentage. In the presence of confounding, the definition of PAR is: Pd(RR−1)/RR, where Pd is the probability of exposure given disease and RR is the multivariate relative risk, estimated here from the mOR. Data were analysed by using SPSS for version 16.0 (SPSS, Chicago, Illinois, USA).

Ethical aspects
Research use of data collected in national registries was authorised by the Ministry of Social Affairs and Health, the Finnish Data Protection Authority and the National Research and Development Center for Welfare and Health.

## RESULTS

### Characteristics of patients and controls

During 1995–2002, national surveillance identified 1282 persons aged 18–49 years with IPI; these patients were included in the case–control study. The median age of patients and their controls was 38.0 years and 67.8% were male.

Overall, 359 (28.0%) patients compared with 743 (5.8%) of control subjects (p<0.001) had an underlying medical condition for which the PPV23 is currently recommended by Finnish public health authorities for asthma; vaccine target groups are similar to those of the US Advisory Committee on Immunization Practices.1 Among the cases, asthma was the second most common underlying condition identified (7.1%) following alcohol-related diseases (11.8%), whereas among controls asthma was the most common underlying condition (2.5%) followed by immunodeficiency or rheumatic diseases and diabetes mellitus (table 1). Overall, 9.4% of cases had a recognised condition or treatment leading to immunosuppression (immunodeficiency or rheumatic diseases, haematological and non-haematological malignancy, HIV infection or diseases of the spleen).

Of the cases, 77 (6.0%) had LRA compared with 302 (2.4%) of the controls; only 14 (1.1%) patients and 12 (0.1%) controls had HRA (table 1). The median duration of hospitalisation for the patients...
with IPI with HRA was 8 days (range, 4–69 days). Of the 77 patients with LRA, 10 (13.0%) had a current indication for PPV23: alcohol-related diseases (n=5), immunodeficiency or rheumatic disease (n=4), non-haematological malignancy (n=2) and chronic liver disease (n=1). No patients with HRA had any underlying conditions. During the 7 and 28 days after the first positive blood or CSF culture, 6/91 (6.6%) and 7/91 (7.7%) of patients with asthma versus 82/1187 (6.9%) and 117/1187 (9.9%) of the other IPI cases died, respectively. All deaths were in the LRA group. The annual incidence of IPI among persons aged 18–49 years with LRA was estimated to be 18.2 cases/100 000 population.

*S pneumoniae* was isolated from blood for 1196 (93.3%) patients and from CSF for 86 (6.7%). Of the 1056 (82.4%) isolates that were serotyped, serotypes 4 (20.8%), 7F (12.1%), 14 (9.7%), 5 (9.0%) and 9V (7.7%) were the most common. Of the serotypes causing IPI, ~90% were covered in PPV23; 76.1% were covered in the paediatric 13-valent pneumococcal conjugate vaccine (table 3). Serotypes in different pneumococcal conjugate vaccine formulations accounted for a larger number of isolates among patients with asthma compared with those without asthma.

### Multivariable analysis

In a conditional logistic regression model adjusted for other risk factors, patients were more likely than controls to have HRA (mOR, 12.3; 95% CI 5.4 to 28.0) and LRA (mOR, 2.8; 95% CI 2.1 to 3.6) (table 2). The adjusted PARs for HRA and LRA were 1% (0.01; 95% CI 0.0055 to 0.017) and 4% (0.069; 95% CI 0.023 to 0.085), respectively. Inclusion of the four patients hospitalised for COPD and their controls in the model did not change the mORs for HRA or LRA (data not shown). We also constructed a second conditional logistic regression model which excluded patients who had immunosuppressive conditions and their controls. The results from this model were similar to the main model: the mOR for HRA was 15.6 (95% CI 6.5 to 37.6) and that for LRA was 2.9 (95% CI 2.2 to 3.9).

### DISCUSSION

Results of our national, population-based study indicate that LRA is also an independent factor moderately increasing the risk for IPI among adults 18–49 years of age. Persons with a recent hospitalisation for asthma (HRA) had a fourfold increased risk of IPI compared with those who had not required hospital care (LRA). Overall, an estimated 5% of the IPI disease burden in the working age adult population was attributable to asthma.

The prevalence of asthma continues to increase globally, and in the USA 16 million (7.3%) adults are estimated to have asthma. Even though accurate assessment of the prevalence is complicated by varying definitions of asthma, an estimated 4.4% of Finnish adults have asthma and the prevalence has increased since the 1960s.

In our study, asthma was the second most common underlying condition among patients with IPI (7.1% of cases). Our findings therefore have important public health implications and support adding medically treated asthma in adults to the list of indications for pneumococcal vaccination which already includes other chronic lung diseases such as COPD and emphysema.

Results from previous studies on whether or not asthma is associated with IPI are limited and have been inconsistent.

No previous data are available from European countries. A recent study among persons aged 2–49 years enrolled in the Medicaid programme in one US state, where cases of IPI identified through active population- and laboratory-based surveillance were linked to administrative data to determine the presence of asthma, suggested that asthma moderately increased the risk of IPI.

However, another recent study in mostly older adults (average age >50 years) analysed administrative data from the US Veteran’s Administration Health Care system and found that compared with control subjects, persons with COPD had an increased risk of hospitalisation for pneumococcal pneumonia but persons with asthma did not. The differences in these study results may be related to the differences in data sources, study populations and their age, definitions used for asthma, outcomes evaluated (IPI being more specific than ICD-coded pneumococcal pneumonia) and analytical methods.

Overall, the findings of our study are largely consistent with the US Medicaid database study, in which persons who had asthma had an overall adjusted OR of 2.4 for IPI compared with control subjects without asthma. However, there were also some important differences. In the US study, high risk patients were defined as those requiring at least one of the following: admission to hospital or emergency department, the use of intensive treatment for acute asthma attacks, long-term corticosteroid use or the dispensing of ≥5 prescriptions for β-agonists within the year before enrolment in the study. These high risk patients accounted for 83% of IPI cases with asthma in the study. Although the OR for HRA (2.6) in the US Medicaid study was not different from the overall OR (2.4), the annual incidence of IPI was estimated to be almost twofold (4.2 vs 2.5 per 10 000 persons) among patients with HRA compared with those with LRA. The association of IPI with LRA

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**Table 2** Association of asthma with invasive pneumococcal infection among persons aged 18–49 years: a conditional logistic regression model

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (N = 1282) n (%)</th>
<th>Controls (N = 12785) n (%)</th>
<th>mOR</th>
<th>95% CI</th>
<th>p Value</th>
<th>PAR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk asthma†</td>
<td>14 (1.1)</td>
<td>12 (0.1)</td>
<td>12.3</td>
<td>5.4 to 28.0</td>
<td>&lt;0.001</td>
<td>0.01</td>
<td>0.0035 to 0.017</td>
</tr>
<tr>
<td>Low risk asthma†</td>
<td>77 (6.0)</td>
<td>302 (2.4)</td>
<td>2.8</td>
<td>2.1 to 3.6</td>
<td>&lt;0.001</td>
<td>0.039</td>
<td>0.023 to 0.055</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>9 (0.7)</td>
<td>1 (&lt;0.1)</td>
<td>96.6</td>
<td>16.6 to 883.9</td>
<td>&lt;0.001</td>
<td>0.0069</td>
<td>0.0016 to 0.012</td>
</tr>
<tr>
<td>Haematological malignancy</td>
<td>25 (2.0)</td>
<td>5 (&lt;0.1)</td>
<td>56.0</td>
<td>20.0 to 157.0</td>
<td>&lt;0.001</td>
<td>0.019</td>
<td>0.010 to 0.028</td>
</tr>
<tr>
<td>Diseases of spleen</td>
<td>2 (0.2)</td>
<td>1 (&lt;0.1)</td>
<td>35.6</td>
<td>3.0 to 428.5</td>
<td>&lt;0.005</td>
<td>0.0015</td>
<td>0.00 to 0.040</td>
</tr>
<tr>
<td>Alcohol-related diseases</td>
<td>151 (11.8)</td>
<td>72 (0.6)</td>
<td>27.2</td>
<td>19.9 to 37.3</td>
<td>&lt;0.001</td>
<td>0.11</td>
<td>0.082 to 0.13</td>
</tr>
<tr>
<td>HIV infection</td>
<td>10 (0.8)</td>
<td>7 (0.1)</td>
<td>14.3</td>
<td>5.3 to 38.5</td>
<td>&lt;0.001</td>
<td>0.0073</td>
<td>0.0018 to 0.013</td>
</tr>
<tr>
<td>Non-haematological malignancy</td>
<td>11 (0.9)</td>
<td>23 (0.2)</td>
<td>5.1</td>
<td>2.4 to 10.9</td>
<td>&lt;0.001</td>
<td>0.0069</td>
<td>0.0016 to 0.013</td>
</tr>
<tr>
<td>Organ or bone marrow transplantation</td>
<td>13 (1.0)</td>
<td>13 (0.1)</td>
<td>2.9</td>
<td>1.0 to 8.8</td>
<td>0.059</td>
<td>0.0067</td>
<td>0.00 to 0.015</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>8 (0.6)</td>
<td>13 (0.1)</td>
<td>2.8</td>
<td>1.0 to 8.2</td>
<td>0.059</td>
<td>0.004</td>
<td>0.00 to 0.010</td>
</tr>
<tr>
<td>Immunodeficiency or rheumatic diseases</td>
<td>56 (4.4)</td>
<td>190 (1.5)</td>
<td>3.1</td>
<td>2.3 to 4.4</td>
<td>&lt;0.001</td>
<td>0.030</td>
<td>0.017 to 0.044</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>45 (3.5)</td>
<td>148 (1.2)</td>
<td>2.3</td>
<td>1.6 to 3.5</td>
<td>&lt;0.001</td>
<td>0.020</td>
<td>0.0076 to 0.034</td>
</tr>
</tbody>
</table>

*Population-attributable risk. The population exposure prevalence is estimated internally from cases—that is, 1.1% for HRA and 6.0% for LRA.
†Hospitalisation for asthma in the past 12 months; four patients hospitalised for chronic obstructive pulmonary disease and their controls were excluded.
‡Entitlement to a prescription drug benefit for asthma but no hospitalisation for asthma in the past 12 months.

mOR, matched odds ratio.
Secondly, although among the national registries we used to obtain data on co-morbidities for IPI cases, the Finnish Cancer Registry has almost 100% coverage.\textsuperscript{20, 21} And the comprehensiveness of the National Hospital Discharge Register data has been validated previously.\textsuperscript{22, 23} It is well known that ICD coding in hospital discharge data may be incomplete and could be subject to misclassification. For this reason, we used hospital discharge data only to identify those underlying conditions for which data were not available in the two other registries (National Social Insurance Institution and Cancer Registry) which use standardised criteria and definitions. Differential diagnosis between reactive airway disease and COPD among middle-aged adults may be difficult and these syndromes may overlap.\textsuperscript{24} Because of the shared reimbursement code, we were unable to distinguish unequivocally between asthma and possible COPD among those who were classified as having LRA, and some misclassification among the two disease entities is possible.\textsuperscript{25} However, the number of IPI cases who may have had COPD in the absence of asthma is likely to be very small in our working age study population with a median age of 38 years.\textsuperscript{26, 27} In addition, misclassification of possible COPD as asthma would probably be non-differential and would therefore make detecting an association more difficult.

Thirdly, we had no information regarding the PPV23 vaccination status of study subjects. However, a recent nationally representative survey among persons 50 years of age and older in Finland found that uptake of PPV23 was extremely low (3%) in the high risk target groups\textsuperscript{28} and only 2.6% of persons aged 18–64 years with asthma or COPD had ever received PPV23 (National Institute for Health and Welfare, unpublished data) making it unlikely that PPV23 vaccination influenced our findings. Fourthly, information on the specific medications of the patients and controls was not available. During 1997–2002, 91.2% of patients 18–49 years of age who were entitled to prescription drug benefits (ie, the LRA group) received a prescription for inhalation and/or oral steroids; 16.9% received oral steroids (NSII, unpublished data).

This population-based study provides further evidence to support an association between asthma and IPI and suggests that, in addition to persons who require hospitalisation and prolonged oral corticosteroid treatment for HRA, those with LRA are also at increased risk of IPI, supporting adding medically treated asthma in adults to the list of indications for pneumococcal vaccination.

Acknowledgements Mikko Virtanen, MSc, is acknowledged for statistical advice.

Competing interests PK received a fee on two occasions (2006 and 2008) for giving a lecture at a symposium organised by Wyeth Finland. The other authors have no competing interests.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

APPENDIX 2: NATIONAL CRITERIA FOR PRESCRIPTION DRUG BENEFITS FOR ASTHMA OR COPD (REIMBURSEMENT OF MEDICATION COST), NATIONAL SOCIAL INSURANCE INSTITUTION (KELA), FINLAND

ONE OF THE FOLLOWING CRITERIA SHOULD BE MET:

Asthma:
1. Diurnal variation in peak expiratory flow (PEF) of >20% over 2 weeks
2. Increase of at least 12% and 200 ml in PEF or forced expiratory volume in 1 s (FEV1) in spirometry after bronchodilator use
3. Increase of at least 15% and 60 l/min (adults) in PEF after bronchodilator use
4. In the corticosteroid test, increase of at least 15% and 200 ml in FEV1, or increase of at least 20% of average PEF measurements during several days
5. Severe or intermediate bronchial reactivity after histamine or methacholine challenge
6. Decrease of at least 15% of PEF or FEV1 during exercise test.

COPD:
1. FEV1 is permanently <40% of the reference value or
2. FEV1 is permanently <50% of the reference value and the need of hospitalisation due to exacerbation of COPD during bronchodilator use or at least two episodes of exacerbation requiring oral corticosteroids or antibiotics.

Drugs included in the prescription drug benefit (reimbursement of cost) for patients with asthma or COPD (2002)
1. Corticosteroids for systemic use
2. Adrenergics, inhalants
3. Inhaled glucocorticoids
4. Inhaled anticholinergics
5. Antiallergics, inhalants (cromoglic acid and nedocromil)
6. Antiasmthics for systemic use (excluding glucocorticoids).

APPENDIX 1: ICD-9* AND ICD-10+ CODES USED IN DEFINING UNDERLYING CONDITIONS FOR DATA IN THE NATIONAL HOSPITAL DISCHARGE DATABASE

<table>
<thead>
<tr>
<th>Underlying condition</th>
<th>ICD-9 codes</th>
<th>ICD-10 codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol-related diseases (Morbus Wernicke, mental, behavioural and neurologic disorders due to alcohol use, hepatic and pancreatic disorders due to alcohol use, toxic effects of alcohol, maternal and fetal care due to alcohol abuse, rehabilitation and counselling due to alcohol abuse)</td>
<td>2851X; 2810A, 2911A, 2913A, 2918A, 2946X, 309X, 3050A, 3518X, 3461A, 3575A, 3594A, 5710A, 5711A, 5712A, 5713X, 5770D, 5771B, 5771C, 5771D, 9800A, 9801A, 9802A, 9803A, 9808X, 9809X, 6554A, 7607A, E850A, V654A</td>
<td>E51.2; F10; G31.2; G40.51; G62.1; G72.1; K70; K86; T51; G03.4; P04.3; X45; Y91; Z50.2; Z71.4</td>
</tr>
<tr>
<td>Cerebrospinal fluid leakage</td>
<td>3498A</td>
<td>G96.0</td>
</tr>
<tr>
<td>Chronic liver diseases (hepatic failure, cirrhosis of liver and biliary ducts, portal hypertension, hepatorenal syndrome and unspecified liver disease)</td>
<td>5709A, 5719X, 5739X, 5715A, 5716A, 5716X, 5719X, 5724A, 5739X</td>
<td>K72; K74; K76.7; K76.9</td>
</tr>
<tr>
<td>COPD</td>
<td>4912B, 4960A</td>
<td>J44</td>
</tr>
<tr>
<td>Diseases of the spleen</td>
<td>2804A, 2859A</td>
<td>D73</td>
</tr>
</tbody>
</table>

*International Classification of Diseases, 9th Revision.
†10th Revision.
COPD, chronic obstructive pulmonary disease.