

# Identification of new risk factors for pneumonia: population-based case-control study

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## ABSTRACT

### Background

Certain conditions are established as risk factors for community-acquired pneumonia. There are a number of other conditions that may also be risk factors, but information on these is limited.

### Aim

To determine new independent risk factors for community-acquired pneumonia using a very large primary care database.

### Design of study

Nested case-control study.

### Setting

Four hundred and forty-three general practices in the UK contributing to the QRESEARCH database.

### Method

A total of 17 172 incident cases of all ages diagnosed with pneumonia between 1996 and 2005 were matched with up to five controls by age, sex, general practice, and calendar year. Associations between pneumonia and each established condition and potential risk factors were determined with odds ratios (ORs), using multiple conditional logistic regression analysis adjusted for smoking, socioeconomic status, and use of influenza and pneumococcal vaccines.

### Results

The analysis confirmed the higher risk of pneumonia among patients with at least one of the established risk factors; the adjusted OR was 2.29 (95% confidence interval [CI] = 2.20 to 2.39). In addition, patients with the following conditions had a higher risk of pneumonia despite adjustment for known risk factors and confounders: stroke or transient ischaemic attack, rheumatoid arthritis, Parkinson's disease, cancers, multiple sclerosis, dementia, and osteoporosis. The adjusted OR for pneumonia among patients without an established risk factor but with at least one of the new conditions was 2.44 (95% CI = 2.24 to 2.65).

### Conclusion

As well as confirming some established risk factors, this study has determined seven new independent risk factors for community-acquired pneumonia.

### Keywords

pneumonia; population; risk factors.

## INTRODUCTION

Community-acquired pneumonia is a serious condition, which affects annually up to 11 per 1000 adults,<sup>1</sup> and up to 40 per 1000 of children.<sup>2</sup> Of these, almost half require hospital admission. *Streptococcus pneumoniae* is the commonest cause of community-acquired pneumonia and can be fatal in up to 20% of cases.<sup>3</sup>

While pneumonia can affect any age group, at most risk are adults aged  $\geq 65$  years, and infants and young children, who do not have a fully developed immune system. Patients at risk include those with splenic dysfunction,<sup>4</sup> cochlear implants or cerebrospinal fluid shunts,<sup>3</sup> chronic cardiovascular disease, chronic pulmonary disease, diabetes,<sup>5</sup> chronic liver disease,<sup>6-8</sup> and chronic renal failure,<sup>5,9</sup> as well as those with HIV and AIDS.<sup>10,11</sup> The 23-valent pneumococcal immunisation has been recommended since 1992 for individuals at high risk of invasive pneumococcal disease, and in 2003 the recommendation was extended to include all people aged  $\geq 65$  years. Pneumococcal vaccination rates have increased over time as a consequence.<sup>12</sup> However, there might be other patients who are at increased risk of pneumonia with conditions that are not included in the vaccine guidelines. Equally, some of those in established risk groups included in the guidelines may not actually be at high risk, since evidence is limited for some of the

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specified risk groups. Patients with rheumatoid arthritis, for example, are not included in the guidance although they seem to be susceptible to pneumococcal disease.<sup>13,14</sup> Pneumonia is also the most common cause of death in patients with acute stroke,<sup>15</sup> and it occurs more frequently than expected in dementia patients,<sup>7,16</sup> and in patients with solid cancers.<sup>11,17,18</sup>

Given the uncertainty regarding the effectiveness of pneumococcal vaccination,<sup>19</sup> and in the presence of increasing morbidity due to pneumonia, GPs need to be able to identify and closely monitor those patients at highest risk of pneumonia. For example, such patients might benefit from earlier intervention with antibiotics when they present to their GP with a chest infection.<sup>20</sup> Better understanding about high-risk groups for pneumonia could also help inform future development of an effective vaccine to prevent pneumonia.

The main aim of this study is to identify additional independent risk factors for community-acquired pneumonia, which could potentially be used in clinical practice to guide treatment decisions.

## METHOD

### *Study design and setting*

A nested case-control study was conducted using general practices in the UK contributing to the QRESEARCH database (version 11, downloaded August 2006). The study period was the 10 years between 1 January 1996 and 31 December 2005.

### *Study population*

An open cohort of patients registered at any time between 1 January 1996 and 31 December 2005, excluding temporary residents, was identified. For each patient, a left censor date was determined, which was the latest of the start of the study: 1 January 1996; the date of patient registration with the practice; or the date of the installation of the EMIS computer system. A right censor date was also defined, which was the earliest of the following: date of diagnosis of the outcome of interest; date of death; date of leaving the practice; date of the latest download of data; or 31 December 2005.

### *Cases of pneumonia*

Patients with an incident diagnosis of pneumonia were identified — that is, patients with a first diagnosis during the 10-year study period (a list of diagnostic codes is available from the authors). Patients with a postmortem diagnosis were included as cases, but patients with a diagnosis prior to their entry into the cohort were excluded.

### *Selection of controls*

Each case was matched to five controls who were

## *How this fits in*

Patients with diabetes, chronic heart disease, chronic renal disease, chronic respiratory disease, asplenia, cerebrospinal fluid shunt, chronic liver disease, sickle cell disease or coeliac disease, cochlear implant, HIV/AIDS, or immunosuppression are at increased risk of invasive pneumococcal disease and therefore are recommended by the Department of Health for pneumococcal vaccination in England. Patients with other conditions including stroke or transient ischaemic attack, rheumatoid arthritis, Parkinson's disease, cancers, multiple sclerosis, dementia, and osteoporosis also have about two- to threefold increase of risk of all causes community-acquired pneumonia and these conditions therefore should be considered as a high-risk patient group.

alive and registered with the practice where the case was registered at the time of diagnosis of each case. Controls were matched on age at index date (to within 1 year), sex, practice, and calendar time. Selection of controls was made without replacement. Controls were allocated an index date, which was the date on which their matched case was first diagnosed with pneumonia.

Patients aged >5 years were included in the analysis if they had at least 5 years of electronic health records available. Children ≤5 years old were included in the analysis if they had complete health records since their birth. This was to ensure the data for vaccinations, prescriptions, and morbidity were as complete as possible over a 5-year period.

### *Risk groups from current guidance*

'Established risk factors' were based on those patients identified as being at high risk of invasive pneumococcal disease according to the Chief Medical Officer's guidance for 2006.<sup>21</sup> The following diseases were included: diabetes, chronic heart disease, chronic renal disease, chronic respiratory disease, asplenia, cerebrospinal fluid shunt, chronic liver disease, sickle cell or coeliac disease, cochlear implant, HIV/AIDS, and immunosuppression. Immunosuppression did not include patients already identified as being at high risk due to the other diseases in the list.

In addition, the risk was estimated in patients with chronic heart disease but without ischaemic heart disease, in patients with treated asthma, and in patients with asthma but no evidence of treatment ('untreated asthma'). Asthma treatment was defined as at least one prescription for a  $\beta$  agonist and/or at least one inhaled steroid within the preceding 12 months.

### *New potential risk groups*

The risk of pneumonia was determined in patients with other morbidities including the following: stroke or transient ischaemic attack, rheumatoid arthritis,

Parkinson's disease, five common cancers (breast, colon, gastric, lung, prostate), multiple sclerosis, dementia, osteoporosis, and osteoarthritis.

These diseases were chosen either because they limit the mobility of patients, which might in turn increase the risk of pneumonia, or because they tend to be associated with immunosuppression.

Patients were considered to be in a current or new disease risk group if they had an appropriate Read code group in their electronic health record before the date of diagnosis of pneumonia, for cases, or before the matched index date, for controls.

### Statistical analysis

All the available cases on the QRESEARCH database who met the inclusion criteria were used, in order to maximise the power of the study. Five matched controls were used per patient, since using more controls than this does not tend to increase the study power.<sup>22</sup> In order to detect an odds ratio (OR) of 1.50 (which was predefined as being clinically important) at 1% significance with 80% power for a condition that occurs in 0.5% of controls, a sample size of 13 500 cases and 67 500 controls would be needed.

Conditional logistic regression was used to

estimate OR with 95% confidence intervals (CIs) for pneumonia. A number of different models were used. First, the unadjusted OR for risk of pneumonia was determined for each of the disease risk groups (both current and potential). Then the OR associated with each disease risk group was determined, adjusting for the potential confounding effects of material deprivation (Townsend deprivation score in fifths based on the output area associated with the patient's postcode), smoking status (current smoker, not current smoker, smoking not recorded), use of influenza vaccine in the 12 months prior to the index date, and number of years of electronic data available prior to the index date (categorised as 5, 6, 7, 8, 9,  $\geq 10$  years). All current disease groups were also adjusted for, and any new potential disease groups that had an unadjusted OR  $\geq 1.5$  were included. As patients aged 5–64 years are not recommended for routine pneumococcal vaccination, the same analyses were performed restricted to such cases and controls.

An additional model included pneumococcal vaccination (categorised as: no recorded pneumococcal vaccination in last 5 years; vaccinated  $\geq 49$  months ago; vaccinated 12–48 months ago;

**Table 1. Distribution of diagnoses with the pneumonia outcome.**

		Cases unrestricted, <i>n</i>	% of total cases ( <i>n</i> = 34 098)	Cases restricted to 5 years of records, <i>n</i>	% of total cases ( <i>n</i> = 17 172)
H2	Pneumonia and influenza	814	2.4	379	2.2
H21	Lobar (pneumococcal) pneumonia	3083	9.0	1733	10.1
H21-1	Chest infection — pneumococcal pneumonia	90	0.3	46	0.3
H22	Other bacterial pneumonia	359	1.1	221	1.3
H22-1	Chest infection — other bacterial pneumonia	137	0.4	86	0.5
H223	Pneumonia due to streptococcus	166	0.5	86	0.5
H22yz	Pneumonia due to bacteria NOS	597	1.8	318	1.9
H22z	Bacterial pneumonia NOS	1072	3.1	709	4.1
H23-1	Chest infection — pneumonia organism OS	2	0.0	0	0
H25	Bronchopneumonia due to unspecified organism	3872	11.4	1652	9.6
H25-1	Chest infection — unspecified bronchopneumonia	900	2.6	330	1.9
H26	Pneumonia due to unspecified organism	12 569	36.9	6160	35.9
H260	Lobar pneumonia due to unspecified organism	5366	15.7	2706	15.8
H261	Basal pneumonia due to unspecified organism	1580	4.6	855	5.0
H262	Postoperative pneumonia	61	0.2	40	0.2
H270	Influenza with pneumonia	81	0.2	29	0.2
H270-1	Chest infection — influenza with pneumonia	9	0.0	3	0.0
H2700	Influenza with bronchopneumonia	67	0.2	20	0.1
H2701	Influenza with pneumonia, influenza virus identified	2	0.0	2	0.0
H270z	Influenza with pneumonia NOS	18	0.1	9	0.1
H28	Atypical pneumonia	1301	3.8	663	3.9
H2y	Other specified pneumonia or influenza	290	0.9	160	0.9
H2z	Pneumonia or influenza NOS	1662	4.9	965	5.6

NOS = not otherwise specified.

vaccinated 15–365 days ago; and vaccinated 1–14 days ago).

Key analyses were repeated, restricted to cases and controls where the index date was prior to 2003 (the year in which pneumococcal vaccine was recommended to all patients aged  $\geq 65$  years), and to cases and controls with at least 10 full years of electronic prescribing records available. The analyses were also repeated restricted to cases with lobar and pneumococcal pneumonia and their controls, as those diagnoses were most likely made on hospital discharge. STATA (version 10) was used for all the analyses. Given the large number of comparisons being undertaken, a *P* value of 0.01 or less was considered statistically significant. A priori, an OR $\geq 1.5$  was considered to be clinically important.

Missing data for smoking status and Townsend deprivation score were analysed as a separate category. As records for children younger than 15 years hardly contained information about smoking status, they were assumed to be non-smokers. The analyses were also repeated considering smoking status in children as not recorded.

## RESULTS

### Incidence rates of pneumonia

There were 443 QRESEARCH practices included in

the analysis. Overall there were 34 098 incident cases of pneumonia arising from 29 605 328 patient-years, giving an overall incidence rate of 115 per 100 000 patient-years.

The incidence of pneumonia varied by year and age group, approximately doubling between 1996 and 2005 in all age groups and reaching an age–sex-standardised rate of 150 cases per 100 000 in 2005. The incidence rate was highest in patients aged  $\geq 75$  years, next highest in patients aged 0–4 years, and lowest in patients aged 15–44 years. Of all the cases of pneumonia, 25% had lobar or pneumococcal pneumonia. The distribution of specific diagnoses in all cases with pneumonia is presented in Table 1. There were 17 172 cases with at least 5 years of prior data, and these were included in the remaining analyses. Of these 4485 (26%) had lobar or pneumococcal pneumonia.

### Baseline characteristics of pneumonia cases and controls

Table 2 shows baseline characteristics for cases with pneumonia and their matched controls. Cases and controls were well balanced with respect to the length of longitudinal records available prior to the index date. Smoking was more common among cases than controls, and there was a slight tendency

**Table 2. Characteristics of cases with pneumonia and age–sex–practice–calendar year-matched controls.**

Characteristics	Cases (n = 17 172)	Controls (n = 71 399)	Adjusted <sup>a</sup> OR (95% CI)
Sex, n (%)			
Males	8714 (50.7)	36338 (50.9)	
Females	8458 (49.3)	35061 (49.1)	
Age band, years, n (%)			
0–4	2949 (17.2)	13934 (19.5)	
5–14	811 (4.7)	3028 (4.2)	
15–44	2173 (12.7)	7450 (10.4)	
45–64	3124 (18.2)	12905 (18.1)	
65–74	2662 (15.5)	11597 (16.2)	
$\geq 75$	5453 (31.8)	22485 (31.5)	
Median (IQR) months of electronic data available	83 (65–111)	83 (64–111)	
Deprivation, n (%)			
Townsend fifth 1 most affluent	3322 (19.3)	14945 (20.9)	1.00
Townsend fifth 2	3269 (19.0)	14593 (20.4)	1.00 (0.95 to 1.06)
Townsend fifth 3	3303 (19.2)	13665 (19.1)	1.08 (1.02 to 1.15)
Townsend fifth 4	3224 (18.8)	12449 (17.4)	1.18 (1.11 to 1.25)
Townsend fifth 5 most deprived	3553 (20.7)	13123 (18.4)	1.27 (1.19 to 1.36)
Townsend missing	501 (2.9)	2624 (3.7)	
Smoking status, <sup>b</sup> n (%)			
Non-smoker	11999 (69.9)	52367 (73.3)	1.00
Smoker	3299 (19.2)	8883 (12.4)	1.61 (1.53 to 1.69)
Smoking status not recorded	1875 (10.9)	10158 (14.2)	
Influenza vaccination in prior 12 months, n (%)	6535 (38.1)	23997 (33.6)	1.39 (1.32 to 1.46)
Pneumococcal vaccination in prior 60 months, n (%)	2821 (16.4)	10263 (14.4)	1.08 (1.02 to 1.14)

<sup>a</sup>Adjusted for the confounding factors listed in the Table. <sup>b</sup>Children <15 years old were considered as non-smokers. IQR = interquartile range. OR = odds ratio.

**Table 3. Characteristics of cases and matched controls and odds ratios for pneumonia for diseases currently and potentially considered as risk factors for pneumococcal disease, all patients.**

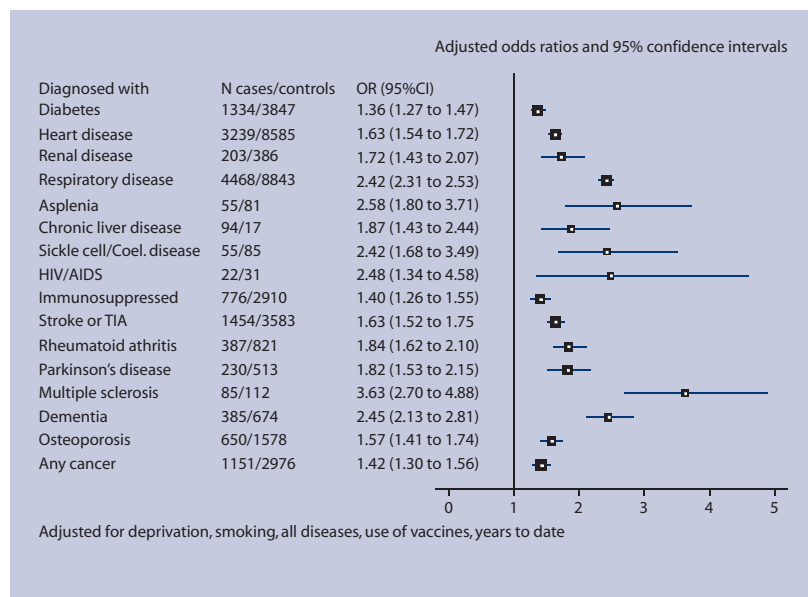
	Cases (n = 17 172), n (%)	Controls (n = 71 399), n (%)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
<b>Current risk factors</b>				
Diabetes	1344 (7.8)	3847 (5.4)	1.54 (1.44 to 1.65)	1.36 (1.27 to 1.47)
Chronic heart disease	3239 (18.9)	8585 (12.0)	1.91 (1.81 to 2.00)	1.63 (1.54 to 1.72)
Ischaemic heart disease	2329 (13.6)	6984 (9.8)	1.54 (1.46 to 1.63)	
CHD, no IHD	910 (5.3)	1604 (2.2)	2.53 (2.31 to 2.76)	
Chronic renal disease	203 (1.2)	386 (0.5)	2.15 (1.81 to 2.56)	1.72 (1.43 to 2.07)
Chronic respiratory disease	4468 (26.0)	8843 (12.4)	2.62 (2.51 to 2.73)	2.42 (2.31 to 2.53)
Treated asthma	2329 (13.6)	4043 (5.7)	2.65 (2.51 to 2.81)	
Untreated asthma	504 (2.9)	1689 (2.4)	1.19 (1.07 to 1.32)	
Asplenia	55 (0.3)	81 (0.1)	2.88 (2.04 to 4.06)	2.58 (1.80 to 3.71)
CSF shunt	11 (0.1)	20 (0.0)	2.24 (1.07 to 4.71)	2.17 (1.00 to 4.69)
Chronic liver disease	94 (0.5)	175 (0.2)	2.24 (1.74 to 2.89)	1.87 (1.43 to 2.44)
Sickle cell or coeliac disease	55 (0.3)	85 (0.1)	2.65 (1.87 to 3.75)	2.42 (1.68 to 3.49)
Cochlear implant	0 (0.0)	3 (0.0)		
HIV/AIDS	22 (0.1)	31 (0.0)	2.71 (1.50 to 4.90)	2.48 (1.34 to 4.58)
Immunosuppressed	776 (4.5)	2910 (4.1)	1.12 (1.03 to 1.21)	1.40 (1.26 to 1.55)
<b>New potential risk factors</b>				
Stroke or TIA	1454 (8.5)	3583 (5.0)	1.86 (1.74 to 1.99)	1.63 (1.52 to 1.75)
Rheumatoid arthritis	387 (2.3)	821 (1.1)	2.02 (1.79 to 2.29)	1.84 (1.62 to 2.10)
Parkinson's disease	230 (1.3)	513 (0.7)	1.87 (1.60 to 2.19)	1.82 (1.53 to 2.15)
Multiple sclerosis	85 (0.5)	112 (0.2)	3.20 (2.40 to 4.26)	3.63 (2.70 to 4.88)
Dementia	385 (2.2)	674 (0.9)	2.41 (2.11 to 2.75)	2.45 (2.13 to 2.81)
Osteoporosis	650 (3.8)	1578 (2.2)	1.84 (1.67 to 2.03)	1.57 (1.41 to 1.74)
Osteoarthritis	2310 (13.5)	8932 (12.5)	1.12 (1.06 to 1.18)	
Any cancer	1151 (6.7)	2976 (4.2)	1.70 (1.58 to 1.82)	1.42 (1.30 to 1.56)
Breast cancer	190 (1.1)	667 (0.9)	1.17 (0.99 to 1.38)	
Colon cancer	107 (0.6)	361 (0.5)	1.23 (0.99 to 1.53)	
Lung cancer	107 (0.6)	98 (0.1)	4.73 (3.58 to 6.25)	
Gastric cancer	16 (0.1)	48 (0.1)	1.38 (0.78 to 2.44)	
Prostate cancer	200 (1.2)	617 (0.9)	1.38 (1.17 to 1.63)	

\*Model includes all current risk factors and any new risk factors with unadjusted odds ratio >1.5, smoking status, Townsend score in quintiles, use of influenza vaccine in last 12 months, use of pneumococcal vaccine in last 5 years (1–14 days, 2–52 weeks, 12–48 months, 49–60 months), number of years of medical records data (5, 6, 7, 8, 9, ≥10). CSF = cerebrospinal fluid. CHD = coronary heart disease. IHD = ischaemic heart disease. OR = odds ratio. TIA = transient ischaemic attack.

**Figure 1. Risk of pneumonia in patients of all ages.**

for cases to be from more deprived areas than controls. Uptake of influenza vaccination in the

preceding 12 months was also marginally higher in cases than controls.



**Risks of pneumonia according to disease risk groups**

Figure 1 and Table 3 show the number of cases and controls with diagnoses for diseases in the established risk groups, and in the potential new risk groups prior to the date of diagnosis of pneumonia in cases, and to the equivalent index date in controls. Almost half of the cases (46%) had been diagnosed with at least one of the diseases in the existing risk groups, compared to 29% of the controls. The unadjusted ORs for all of the current risk factor diseases were >1.5, apart from in the immunosuppressed patient group, where the unadjusted OR was 1.12 (95% CI = 1.03 to 1.21).

For the new potential risk factors, the proportion of cases diagnosed with any of these diseases was significantly higher than among controls. Most of the unadjusted OR were >1.5. Among the cancer patients,

those with lung cancer had the highest unadjusted OR for pneumonia (unadjusted OR: 4.73, 95% CI = 3.58 to 6.25). Multiple sclerosis showed the next highest risk of pneumonia (unadjusted OR: 3.20, 95% CI = 2.40 to 4.26). As the unadjusted OR for osteoarthritis was only 1.12 (95% CI = 1.06 to 1.18), it was excluded from further analysis. More than one-fifth of cases (21.2%) had been diagnosed with at least one of the potential risk factors (stroke or transient ischaemic attack [TIA], rheumatoid arthritis, Parkinson's disease, multiple sclerosis, dementia, osteoporosis, or any type of cancer) compared with 12.6% of controls.

Adjustment for a number of potential confounding variables tended to reduce the OR, with the exception of the immunosuppressed, multiple sclerosis, and dementia groups. The adjusted ORs for all current and potential risk groups were greater than 1.5, except for in the diabetes, immunosuppressed, and any cancer groups. The highest adjusted ORs were for multiple

sclerosis, HIV/AIDS, and asplenia.

Table 4 shows the numbers of patients diagnosed with only a current risk group disease, only a new potential risk group disease, and with diseases from both risk groups. Out of 7894 cases diagnosed with a current risk group disease, 2696 patients (34%) were also diagnosed with at least one of the new potential risk group diseases, and out of 20 985 controls with a current risk group disease, 5957 (28%) also had a new risk group disease. For example, most of the cancer patients (97.6% of cases with cancer and 97.0% of controls) fall into the immunosuppressed group. The adjusted risk of pneumonia in patients with one or more current risk factor conditions but no new risk factors was 2.3-fold increased (OR: 2.33, 95% CI = 2.23 to 2.44) compared with patients with no current or new risk factors. In patients with one or more new potential risk factor conditions (excluding osteoarthritis) and not diagnosed with diseases from

**Online Table 4. Characteristics of cases and matched controls and odds ratios for pneumonia for a number of diseases currently and potentially considered as risk factors for pneumococcal disease, all patients and patients aged 5–64 years.**

	Cases, n (%)	Controls, n (%)	Unadjusted OR (95% CI)	Adjusted <sup>a</sup> OR (95% CI)
All patients (17 172 cases and 71 399 controls)				
Conditions from current and new risk factor lists				
No current or new risk factors	8338 (48.6)	47385 (66.4)	1.00	1.00
Current risk factors only	5198 (30.3)	15028 (21.1)	2.48 (2.37 to 2.59)	2.33 (2.23 to 2.44)
New risk factors only	940 (5.5)	3029 (4.2)	2.51 (2.31 to 2.72)	2.44 (2.24 to 2.65)
Current and new risk factors	2696 (15.7)	5957 (8.3)	3.80 (3.57 to 4.04)	3.59 (3.38 to 3.82)
Conditions from current risk factor list				
Any current risk factor	7894 (46.0)	20985 (29.4)	2.43 (2.34 to 2.53)	2.29 (2.20 to 2.39)
One condition	5878 (34.2)	17431 (24.4)	2.18 (2.09 to 2.27)	2.08 (1.99 to 2.17)
Two conditions	1680 (9.8)	3142 (4.4)	3.93 (3.66 to 4.21)	3.63 (3.38 to 3.90)
Three or more conditions	336 (2.0)	411 (0.6)	6.12 (5.26 to 7.12)	5.64 (4.84 to 6.58)
Conditions from current and new risk factor lists				
Any risk factor	8834 (51.4)	24014 (33.6)	2.71 (2.60 to 2.82)	2.56 (2.45 to 2.68)
One condition	4736 (27.6)	15280 (21.4)	2.26 (2.16 to 2.36)	2.16 (2.06 to 2.26)
Two conditions	2786 (16.2)	6669 (9.3)	3.57 (3.37 to 3.79)	3.37 (3.17 to 3.59)
Three or more conditions	1312 (7.6)	2064 (2.9)	5.85 (5.39 to 6.36)	5.50 (5.05 to 5.98)
Patients aged 5–64 years (6108 cases and 23–383 controls)				
Conditions from current and new risk factor lists				
No current or new risk factors	3807 (62.3)	18487 (79.1)	1.00	1.00
Current risk factors only	1794 (29.4)	3974 (17.0)	2.30 (2.15 to 2.47)	1.96 (1.82 to 2.11)
New risk factors only	166 (2.7)	376 (1.6)	2.49 (2.05 to 3.02)	2.32 (1.91 to 2.82)
Current and new risk factors	341 (5.6)	546 (2.3)	3.65 (3.15 to 4.24)	3.14 (2.69 to 3.66)
Conditions from current risk factor list				
Any current risk factor	2135 (35.0)	4520 (19.3)	2.36 (2.21 to 2.52)	2.01 (1.87 to 2.15)
One condition	1868 (30.6)	4175 (17.9)	2.23 (2.09 to 2.38)	1.94 (1.80 to 2.09)
Two conditions	229 (3.75)	311 (1.33)	4.10 (3.42 to 4.92)	3.05 (2.52 to 3.70)
Three or more conditions	38 (0.62)	34 (0.15)	6.83 (4.22 to 11.0)	5.25 (3.21 to 8.58)
Conditions from current and new risk factor lists				
Any risk factor	2301 (37.7)	4896 (20.9)	2.44 (2.29 to 2.61)	2.10 (1.96 to 2.24)
One condition	1735 (28.4)	4041 (17.3)	2.20 (2.05 to 2.36)	1.93 (1.80 to 2.08)
Two conditions	468 (7.7)	756 (3.2)	3.64 (3.20 to 4.13)	3.01 (2.63 to 3.44)
Three or more conditions	98 (1.6)	99 (0.4)	6.45 (4.79 to 8.67)	5.14 (3.79 to 6.97)

<sup>a</sup>All models include smoking status, Townsend score in quintiles, use of influenza vaccine in last 12 months, use of pneumococcal vaccine in last 5 years (1–14 days, 2–52 weeks, 12–48 months, 49–60 months), number of years of medical records data (5, 6, 7, 8, 9, ≥10). OR = odds ratio.

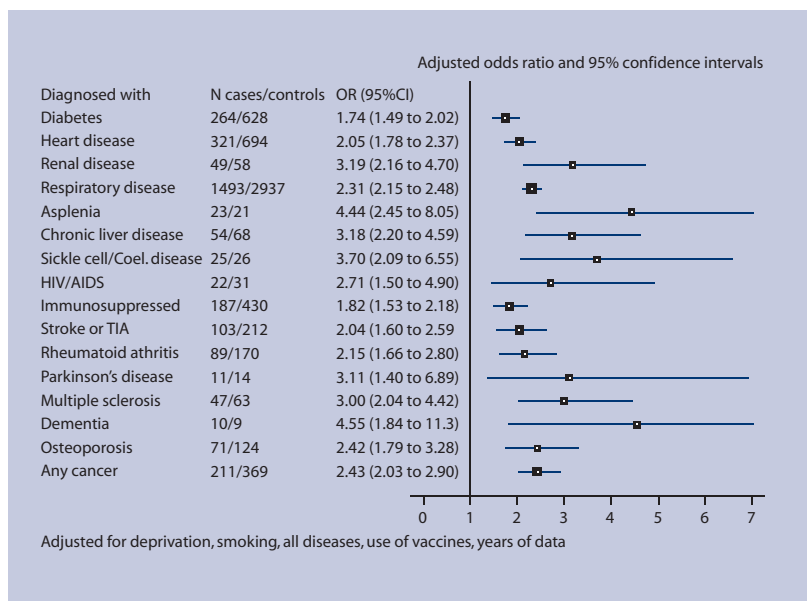


Figure 2. Risk of pneumonia in patients aged 5–64 years.

the current risk group, the risk was almost 2.5-fold increased (OR: 2.44, 95% CI = 2.24 to 2.65) after adjusting for smoking, deprivation, use of influenza vaccine, use of pneumococcal vaccine, and years of medical records.

Table 4 also show how multiple conditions affect the

risk of pneumonia: patients with three or more conditions have a risk almost three times as high as patients with only one condition.

**Restricted analyses**

The analyses were repeated on patients aged 5–64 years. The results were similar to those in patients of all ages. The risk of pneumonia in those with one or more current risk factor diseases and no new risk factor disease adjusted for the confounding variables was twofold increased (OR: 1.96, 95% CI = 1.82 to 2.11), and in those with one or more diseases from the potential risk factor list (excluding osteoarthritis) and not diagnosed with any of the current risk group diseases, it was 2.3-fold increased (OR: 2.32, 95% CI = 1.91 to 2.82). These results are shown in Figure 2 and Table 4.

The analyses also showed similar results to the analyses performed for the whole sample when restricted to: patients aged ≥65 years; patients with pneumonia diagnosed before 2003; and patients with lobar or pneumococcal pneumonia. The increased risk of pneumonia for those patients with at least one of the diseases from the current risk factor list was approximately the same (OR ranged from 2.29 for patients with lobar pneumonia to 2.32 for patients with

**Table 5. Timing of pneumococcal vaccination for all pneumonia cases and for cases with lobar or pneumococcal pneumonia and their matched controls.**

	Cases, n (%)	Controls, n (%)	Adjusted <sup>a</sup> OR (95% CI)
<b>Timing of pneumococcal vaccination before pneumonia diagnosis</b>			
Patients with ≥5 years of medical records (17 172 cases and 71 399 controls)			
No recorded use in last 5 years	14351 (83.6)	61136 (85.6)	1.00
≥49 months ago	476 (2.8)	1525 (2.1)	1.11 (0.98 to 1.25)
12–48 months ago	1604 (9.3)	5457 (7.6)	1.02 (0.95 to 1.10)
15–365 days ago	715 (4.2)	3137 (4.4)	0.83 (0.76 to 0.92)
1–14 days ago	26 (0.2)	144 (0.2)	0.67 (0.43 to 1.04)
Patients with ≥10 years of medical records (6642 cases and 27 294 controls)			
No recorded use in last 10 years	5429 (81.7)	23380 (85.7)	1.00
≥61 months ago	491 (7.4)	1287 (4.7)	1.18 (1.02 to 1.37)
49–60 months ago	106 (1.6)	346 (1.3)	0.93 (0.72 to 1.19)
12–48 months ago	402 (6.1)	1266 (4.6)	1.06 (0.91 to 1.23)
15–365 days ago	202 (3.0)	972 (3.6)	0.71 (0.59 to 0.86)
1–14 days ago	12 (0.2)	43 (0.2)	0.95 (0.48 to 1.87)
<b>Timing of pneumococcal vaccination before diagnosis of lobar or pneumococcal pneumonia</b>			
Patients with ≥5 years of medical records (4485 cases and 18 596 controls)			
No recorded use in last 5 years	3792 (84.6)	16135 (86.8)	1.00
≥49 months ago	124 (2.8)	351 (1.9)	1.23 (0.97 to 1.56)
12–48 months ago	387 (8.6)	1279 (6.9)	1.05 (0.91 to 1.21)
15–365 days ago	173 (3.9)	794 (4.3)	0.82 (0.67 to 1.00)
1–14 days ago	9 (0.2)	37 (0.2)	0.98 (0.45 to 2.14)
Patients with ≥12 months of medical records (7502 cases and 34 941 controls)			
No recorded use in last 12 months	7199 (96.0)	33615 (96.2)	1.00
15–365 days ago	290 (3.87)	1260 (3.61)	0.88 (0.76 to 1.02)
1–14 days ago	13 (0.17)	66 (0.19)	0.76 (0.41 to 1.43)

<sup>a</sup>ORs (odds ratios) are adjusted for one or more current risk factors, one or more new potential risk factors, smoking status, Townsend score in quintiles, use of influenza vaccine in last 12 months, number of years of medical records data (5, 6, 7, 8, 9, 10).

pneumonia diagnosed before 2003). The increased risk of pneumonia for patients with at least one disease from the new potential risk factor list and without diseases from the current risk factor group varied slightly (OR ranged from 1.94 for patients with lobar pneumonia to 2.50 for patients aged  $\geq 65$  years and patients diagnosed before 2003).

### **Pneumococcal vaccination**

Table 5 shows the number of cases and controls vaccinated with pneumococcal vaccine. Only 16.4% of cases and 14.4% of controls had records of pneumococcal vaccination in the last 5 years. Among the patients with at least 10 years of medical records, the proportion of cases who had been vaccinated in the last 10 years was 18.3%, and the proportion of controls was 14.3%. Table 5 shows results from adjusted analyses for time since the last vaccination in individuals with at least 5 and 10 years of data. There was a significantly lower risk of pneumonia in patients who had been vaccinated between 15 and 365 days previously, compared with those not vaccinated in the last 5 years (OR 0.83, 95% CI = 0.76 to 0.92), but not in patients vaccinated more than 12 months earlier.

Table 5 also shows the results of the analysis regarding the use of pneumococcal vaccine, but restricted to patients with lobar or pneumococcal pneumonia. The adjusted OR were similar to those for all pneumonia cases, although they were not statistically significant at the 1% significance level.

All the analyses were performed assuming missing smoking status for children aged  $< 15$  years as non-smokers. Exactly the same results were obtained for all analyses, assuming smoking status for children as not recorded.

## **DISCUSSION**

### **Summary of main findings**

This is a large population-based case-control study designed to determine risk factors for community-acquired pneumonia. Overall, the study has shown that diagnoses of pneumonia are about two to three times more common in individuals in any of the specified clinical risk groups (both existing and new risk groups) than in individuals without these conditions. Similar results were obtained for subgroup analyses on patients with more specific diagnoses of lobar or pneumococcal pneumonia.

The increased risk of all-cause pneumonia among patients in existing risk groups persisted despite adjustment for the potential confounding effects of deprivation, smoking, and influenza and pneumococcal vaccination (OR: 2.29 in patients with one or more current risk factor diseases). This analysis, therefore, reinforces existing risk groups which include patients with diabetes, chronic heart

disease, chronic renal disease, chronic respiratory disease, asplenia, cerebrospinal fluid shunt, chronic liver disease, sickle cell disease, coeliac disease, cochlear implant, HIV/AIDS, or immunosuppression.

The new risk groups identified in this study include patients with stroke or transient ischaemic attack, rheumatoid arthritis, Parkinson's disease, cancers, multiple sclerosis, dementia, and osteoporosis. Overall, a 2.5-fold increased risk of all-cause pneumonia was found among patients with one or more of these new risk factors, taking into account known risk factors and potential confounding variables (OR: 2.44). Patients with lung cancer and multiple sclerosis have particularly high increased risk of pneumonia, with fivefold and threefold increased risks respectively. The magnitude of these risks exceeds that observed for the majority of existing risk groups.

The study also showed some effectiveness of the pneumococcal vaccine, decreasing the risk of pneumonia by 17% (OR: 0.83, 95% CI = 0.76 to 0.92), and only if the vaccine was administered within the year before the index date. This effect is not large and is not protective enough for the general population; therefore, taking into account other risk factors is essential in preventing pneumonia. A similar conclusion was reached in a systematic review and meta-analysis based on 22 randomised control trials showing no significant preventive effect of pneumococcal vaccination.<sup>23</sup>

This is a unique study in the community setting looking at the effect of comorbidities on the risk of pneumonia. British Thoracic Society guidelines recognised such conditions as asplenia, sickle cell and coeliac disease, renal disease, heart disease, lung disease, liver disease, diabetes, and immunosuppression due to HIV infection;<sup>1</sup> and these diseases are included in the vaccine guidelines. This study has not only confirmed that patients with current risk group conditions have an increased risk of pneumonia, but has also demonstrated that there is an additional group of patients who are not recommended for pneumococcal vaccination but have an increased risk of pneumonia.

### **Strengths and limitations of the study**

The study has several strengths. The QRESEARCH database has been validated (<http://www.qresearch.org>) and covers a large representative population from primary care, so the results are likely to be generalisable to the rest of the UK. As the study is based on computer-recorded prescribing and morbidity data collected prospectively, it was possible to include all eligible patients (including those who had died), thereby avoiding selection bias.

Matching of controls to cases on age, sex, calendar



time, and practice removed confounding by these factors. The analysis was also adjusted for smoking, deprivation, and influenza and pneumococcal vaccinations, to minimise the potential confounding effects of these variables. In contrast to studies based on questionnaire or interview data, there is no recall bias, since information about the patient and morbidities, as well as exposure to pneumococcal vaccine, was prospectively recorded on computer before the diagnosis of pneumonia was made and so is unaffected by the pneumonia diagnosis itself. Any bias due to misclassification is likely to be minimal, because recording of clinical diagnosis and use of prescribed medications in general practice has been shown to have high levels of accuracy and completeness.<sup>24</sup>

The study had some limitations — information on certain risk factors for pneumonia such as use of alcohol is less consistently recorded in patient electronic health records and so has not been included in the analysis. The study has, however, included liver disease, which could be viewed as a proxy for chronic alcohol use. As with all observational studies, there could be residual confounding which it is not possible to fully correct.

The increased risk of pneumonia in the previously identified and newly identified risk groups could be a reflection of consulting bias, where pneumonia is opportunistically diagnosed when patients consult for one of these conditions. However, given that pneumonia is a serious diagnosis, it is unlikely that such a diagnosis would be made by chance in a patient consulting for another reason.

The other limitation is that the diagnosis of pneumonia was recorded by a GP and quite often was not supported by chest X-ray examination. However, British Thoracic Society guidelines do not consider chest radiograph as a necessary investigation for such patients in the community, relying instead on clinical symptoms of pneumonia.<sup>1</sup> However, a GP's knowledge of a patient's comorbidities might alter the likelihood of making the diagnosis of pneumonia. This is a potential source of diagnostic bias which cannot be controlled for.

#### Comparison with existing literature

The pneumonia incidence rates have increased over time, which is consistent with trends of hospital admissions for pneumonia,<sup>25</sup> but contrasts with trends in incidence data reported by the Royal College of General Practitioners (RCGP),<sup>26</sup> which have shown a consistent decline. More detailed comparisons, however, between QRESEARCH and RCGP data show that, when similar definitions of pneumonia are used, the rates are comparable, suggesting that some of the difference is due to differences in data capture

and case definition (D Fleming, personal communication, 2007). The definitions of pneumonia in the present analyses, for example, include post-mortem diagnoses and diagnoses entered retrospectively after discharge from hospital, whereas the RCGP data only include contemporaneous diagnoses made during GP consultations.

#### Implications for clinical practice and future research

In addition to confirming some 'established risk factors', this study has identified seven new independent risk factors for all-cause community-acquired pneumonia. The results of this study could help clinicians identify patients at higher risk of pneumonia and also help inform future vaccine development given the possible lack of efficacy of the 23-valent vaccine against pneumonia. Further research would be needed to determine whether these high-risk patient groups would benefit from early intervention with antibiotics in the event of a respiratory infection or during a flu epidemic.

#### Funding body

The project was funded by the Health Protection Agency.

#### Ethics committee

This project was approved by the QRESEARCH scientific board for approval and was notified to the Trent Multi Centre Research Ethics Committee, reference number MREC/03/4/021

#### Competing interests

Julia Hippisley-Cox is university professor and co-director of QRESEARCH — a not-for-profit organisation which specialises in the independent academic analysis and research of primary care health data. QRESEARCH is a joint venture between the University of Nottingham and EMIS (commercial supplier of 60% of primary care systems in use in the UK)

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#### Discuss this article

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