# Aetiology and prediction of pneumonia in lower respiratory tract infection in primary care

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## ABSTRACT

### Background

Knowledge of predominant pathogens and their association with outcome are of importance for the management of lower respiratory tract infection (LRTI). As antibiotic therapy is indicated in pneumonia and not in acute bronchitis, a predictor of pneumonia is needed.

### Aim

To describe the aetiology and outcome of LRTI in adults with pneumonic and adults with non-pneumonic LRTI treated in general practice and to identify predictors of radiographic pneumonia.

### Design of study

Prospective, observational study.

### Setting

Forty-two general practices and an outpatient clinic at Odense University Hospital, Denmark.

### Method

A total of 364 adults diagnosed with community-acquired LRTI by their GP were studied with chest radiography, vital signs, biochemical markers of inflammation (C-reactive protein [CRP] and leukocyte count), and microbiological examinations. Primary outcome measure was hospitalisation within 4 weeks.

### Results

Pneumonia was radiographically verified in 48 of 364 patients (13%). Bacterial infection was seen more often in patients with pneumonia (33% versus 17%, $P<0.001$), and viral infection more often in non-pneumonic patients (26% versus 13%, $P<0.05$). Hospitalisation was more common in patients with pneumonia compared to non-pneumonic patients (19 versus 3%, $P<0.001$); and in patients with pneumococcal infection compared with patients without pneumococcal infection (26 versus 4%, $P = 0.001$). The positive predictive value of GPs' diagnosis of pneumonia was low (0.23), but the vital signs, CRP, and leukocyte count had comparably low positive predictive values (0.23–0.30).

### Conclusion

*Streptococcus pneumoniae* was the most common bacterial pathogen. The risk of hospitalisation was highest among patients with pneumonia or pneumococcal infection; this emphasises the importance of coverage of *S. pneumoniae* when treatment is indicated. CRP should not be introduced for diagnosis of radiographic pneumonia in general practice before its use has been investigated in prospective, controlled intervention trials using CRP-guided treatment algorithms.



### Keywords

pneumonia; primary health care; respiratory tract infections.


## INTRODUCTION

The incidence of lower respiratory tract infection (LRTI) in primary care varies between studies due to differences in population characteristics, and the lack of a gold standard for the diagnosis. In a UK study, the incidence in adults was estimated to be 44 cases per 1000 population per year, and the proportion with radiographically-verified pneumonia was 12%.[1] Most patients diagnosed in primary care are treated by GPs. Diagnostic procedures such as chest radiography, sputum, and blood cultures are not usually carried out on a routine basis in general practice. The decision to initiate antibiotic treatment relies on clinical assessment, and the choice of drug relies on the knowledge of the distribution of the most likely pathogens and their resistance patterns in the given patient population. The majority of patients with LRTI are prescribed antibiotics[2–4] despite evidence of the doubtful benefits of antibiotic treatment for acute bronchitis.[5–7] Reasons for prescribing are not always based on clinical indications.[8,9]

There is a general agreement that antibiotic treatment is indicated in most cases of radiographic pneumonia in adults, and identifying this smaller group in the larger group of patients with LRTI could

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## How this fits in

There is no evidence that antibiotics are of benefit to adults with acute bronchitis. Consequently, antibiotic treatment of patients with LRTI (lower respiratory tract infection) should essentially be restricted to patients with pneumonia and patients with severe infectious episodes of acute exacerbation of chronic obstructive pulmonary disease. In this study, elevated C-reactive protein (CRP) was the best independent predictor of radiographic pneumonia, but not superior to the GPs' clinical diagnosis. *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* were the bacteria most commonly detected. Patients with verified pneumonia and patients with pneumococcal infection had the highest risk of subsequent hospitalisation. This emphasises the importance of an empiric antibiotic treatment covering *S. pneumoniae* when treatment is indicated.

reduce the use of antibiotics. No constellations of symptoms or clinical findings has been found to predict radiographic pneumonia with sufficient accuracy.[10] The aims of the present study were to investigate the incidence of possible pathogens involved in LRTI within a well-defined population, to compare the findings in patients with and without pneumonia, to investigate whether any particular pathogens were associated with treatment failure leading to hospitalisation, and to evaluate simple vital signs and biochemical markers of inflammation as predictors of radiographic pneumonia in patients with LRTI in primary care.

### Box 1. Inclusion and exclusion criteria

- Inclusion criteria
  - Age ≥18 years
  - A GP's diagnosis of lower respiratory tract infection (initial consultation)
- Exclusion criteria
  - Hospitalisation in the preceding 7 days
  - Severity of illness requiring hospitalisation (according to the GP)
  - Pregnancy
  - Former participation in the study

### Box 2. Karnofsky performance status score.

| Score | Functional status |
|---|---|
| 80–100 | ▶ Able to work and carry out normal activity: no special care needed |
| 50–70 | ▶ Unable to work; able to live at home and care for most personal needs; varying amounts of assistance needed |
| 10–40 | ▶ Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly |
| 0 | ▶ Dead |

## METHOD

### Setting

This prospective study took place in Odense, a Danish university city with 185 000 inhabitants. The study periods were 9 September — 1 November 2002, and 6 January — 25 April 2003. The 119 GPs serving the area were invited to participate, and 42 accepted.

### Study population

In the study periods, GPs consecutively registered all patients with LRTI fulfiling the inclusion criteria and having no exclusion criterion (Box 1). To mimic the daily clinical situation, it was left to the GPs to make the diagnosis of LRTI. Patients accepting active participation (active participants) were examined within a few hours at the outpatient clinic of infectious diseases at Odense University Hospital. Initiation of antibiotic therapy and control of treatment was managed by the GPs. Patients were asked not to take any newly prescribed antibiotics until after their visit to the outpatient clinic.

### Registration and examinations

For all patients, GPs registered sex, age, smoking habits, influenza and pneumococcal immunisation status, underlying illnesses, respiratory symptoms and signs, presumptive diagnosis (pneumonia, acute bronchitis, or acute exacerbation of chronic obstructive pulmonary disease), and type of antibiotic treatment (if prescribed), by filling in a form.[11] Active participants were interviewed by a research nurse at the outpatient clinic regarding symptoms, underlying illnesses, smoking habits, immunisation status, and antibiotics taken within the previous 8 days. To asses the habitual functional status of the patients, the pre-morbid Karnofsky performance status score was registered (Box 2;[12] Supplementary Box 1). This assesses the level of assistance needed in daily living, and for those who are able to care for themselves, the degree of effort needed to cope. Sputum was obtained either by spontaneous expectoration or by the aid of nebulised saline. Blood and sputum were cultured, and the latter was also analysed with polymerase chain reaction (PCR) for influenza A and B viruses, respiratory syncytial virus (RSV), parainfluenza virus type 3, adenovirus, rhinovirus, human metapneumovirus (HMPV), *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae/psittaci*. A chest radiograph was taken and evaluated by an experienced specialist in infectious lung diseases, who was blinded to all other study information. Pneumonia was defined by the finding of a transient, non-malignant infiltrate. Respiratory rate, heart rate, temperature, and arterial oxygen saturation ($SATO_2$) measured by pulse oximetry were registered. C-reactive protein (CRP) and

leukocyte count were measured. GPs received all results after they had reached a decision about the need for antibiotic therapy.

### Outcome measures and predictor variables

Patients returned for a follow-up interview 4 weeks after enrolment. Non-elective admittance to hospital, antibiotic treatment, and the Karnofsky performance status score at day 28 were registered. Patients with infiltrates at enrolment had a second chest radiograph taken to confirm resolution of the infiltrate. Included were the following vital signs and inflammatory markers as predictor variables for radiographic pneumonia, as they are potentially available in GPs' consultation: heart rate (<100 BPM versus ≥100 BPM), respiratory rate (<22 breaths per minute versus ≥22 breaths per minute), $SATO_2$ ≤95% versus >95%), rectal temperature (<38°C versus ≥38°C), CRP (<20 mg/l versus ≥20 mg/l), and leukocyte count (<10 million/ml versus ≥10 million/ml).

### Statistical methods

Data were analysed using STATA 8.0. To compare categorical variables, Fisher's Exact test was used. Continuous variables were compared using the Mann–Whitney two-sample rank sum test. Level of significance was set at $P<0.05$ in a two-tailed test. To adjust for confounders, a logistic regression model was used for categorical outcomes. Sensitivity and positive predictive value (PPV) of the predictor variables were calculated. In the analysis of radiographic pneumonia, logistic regression was used to estimate prevalence odds ratios (OR) and associated 95% confidence intervals. In analysis of each of the above-mentioned predictor variables, the other variables were included as potential confounders. Selection of confounders was performed using the 'change in estimate' method and only factors changing the OR by at least 10% were included in the final model.[13]

## RESULTS

### Patient characteristics

Patients with LRTI ($n$ = 693) were registered by 42 GPs (Figure 1). Of these, 369 patients (53%), were examined at the outpatient clinic. Reasons for non-participation for the remaining 324 were: indisposition or unwillingness to come to the clinic, 151 (47%); inability to come to the clinic before closing time, 99 (31%); and other reasons, 74 (23%). According to GPs' registrations, non-participants differed from active participants in having less dyspnoea, less tachycardia, and being prescribed more antibiotics at the initial consultation. There was no statistical significant difference between non-participants and active participants regarding age, sex, underlying illnesses, smoking habits, presumptive diagnosis, or the presence of fever (Table 1).

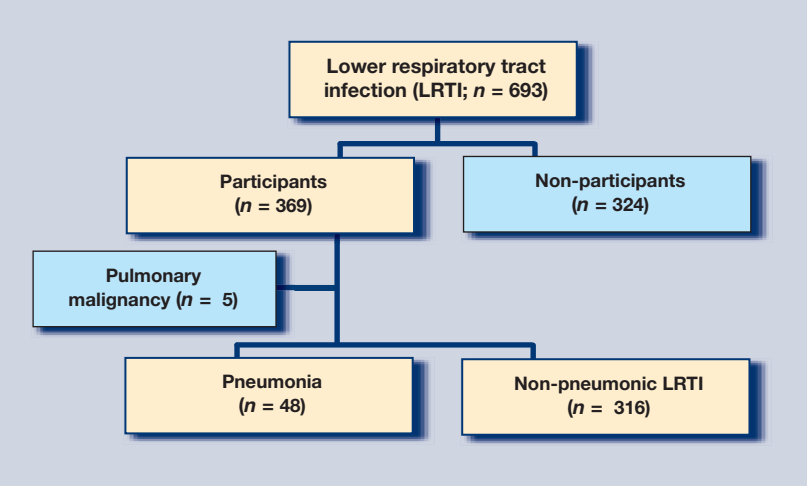


*Figure 1. Patients screened for participation.*

Five active participants (1.4%) were excluded from the study before analysing the data because the initial radiographic findings were strongly suggestive of malignancy, which was later confirmed in all cases.

GPs' presumptive diagnoses were available for 345 (95%) of the active participants. Pneumonia was the clinical diagnosis in 122 patients (35%). Characteristics of the 364 active participants are shown in Table 2.

**Table 1. Baseline characteristics of participants and non-participants registered by GPs.**

| | Participants[a] ($n$ = 358), % | Non-participants ($n$ = 324), % |
|---|---|---|
| Median age, years | 50 | 52 |
| Sex, male | 47 | 40 |
| Current smoker | 43 | 36 |
| Former smoker | 17 | 15 |
| Influenza immunisation | 13 | 10 |
| Pneumococcal immunisation | 4 | 5 |
| Chronic obstructive pulmonary disease | 11 | 16 |
| Any underlying disease | 34 | 40 |
| Cough | 98 | 97 |
| Dyspnoea | 54 | 42 |
| Sputum production | 71 | 69 |
| Tachypnoea (respiratory rate >20/min) | 14 | 13 |
| Tachycardia (heart rate >100/min) | 10 | 5 |
| Temperature >37.5°C | 43 | 42 |
| Abnormal auscultation | 37 | 38 |
| Diagnosis, pneumonia | 35 | 31 |
| Diagnosis, acute bronchitis | 54 | 50 |
| Diagnosis, acute exacerbation of chronic obstructive pulmonary disease | 9 | 13 |
| Antibiotic treatment initiated | 56 | 74 |

[a]*For six participants, GPs' data were missing.*

## Table 2. Patient characteristics, symptoms, and signs in pneumonic patients and patients without pneumonia

| | All patients (*n* = 364) | Pneumonia (*n* = 48) | Non-pneumonic LRTI (*n* = 316) | *P*-value |
|---|---|---|---|---|
| Age in years, median (range) | 50 (18–94) | 61 (22–88) | 48 (18–94) | 0.001 |
| Sex, male | 179 (49) | 28 (58) | 151 (48) | 0.215 |
| Smoking habits | | | | |
| Current smoker | 165 (45) | 16 (33) | 149 (47) | 0.087 |
| Former smoker | 93 (26) | 15 (31) | 78 (25) | 0.375 |
| Never smoked | 106 (29) | 17 (35) | 89 (28) | 0.310 |
| Excessive consumption of alcohol[a] | 11 (3) | 2 (4) | 9 (3) | 0.644 |
| Immunisation status | | | | |
| Influenza vaccination | 68/360 (19) | 17 (35) | 51/312 (16) | 0.005 |
| Pneumococcal vaccination | 23/355 (6) | 5/46 (11) | 18/309 (6) | 0.199 |
| Underlying disease[b] | 132 (36) | 21 (44) | 111 (35) | 0.269 |
| Chronic obstructive pulmonary disease | 33 (9) | 10 (21) | 23 (7) | 0.006 |
| Cardiac illness | 31 (9) | 5 (10) | 26 (8) | 0.581 |
| Karnofsky performance status | | | | |
| Score ≥80 prior to the current LRTI[c] | 335 (92) | 43 (90) | 292 (92) | 0.564 |
| Symptoms | | | | |
| Cough[d] | 355 (98) | 47 (98) | 308 (97) | 1.000 |
| Dyspnoea[d] | 263 (72) | 37 (77) | 226 (72) | 0.492 |
| Sputum production[d] | 295 (81) | 33 (69) | 262 (83) | 0.028 |
| Chest pain | 234 (64) | 30 (63) | 204 (65) | 0.872 |
| Abnormal auscultation | 129/352 (37) | 16/47 (34) | 113/305 (37) | 0.747 |

*Except for age, characteristics are expressed as numbers (%). Denominator shown when data were not available for all patients. [a]Excessive alcohol consumption: >24 g/day (women) and >36 g/day (men). [b]Underlying disease: active cancer or cancer diagnosed within 1 year, n = 1; cardiovascular illness (any cardiac illness or hypertension), n = 76; respiratory illness (chronic obstructive pulmonary disease or asthma), n = 55; cerebrovascular illness (former stroke or transitory cerebral ischemia), n = 11; chronic renal or liver dysfunction, n = 4; diabetes, n = 25; other, n = 10. [c]Karnofsky performance status score ≥80 = able to care for self independently. [d]New or increased. LRTI = lower respiratory tract infection.*

## Table 3. Pathogens in pneumonic patients and patients without pneumonia.

| Bacteria | Total (*n* = 364) | Pneumonia (*n* = 48) | Non-pneumonic LRTI (*n* = 316) | *P*-value |
|---|---|---|---|---|
| *Streptococcus pneumoniae* | 23 (6) | 7 (15) | 16 (5) | 0.021 |
| *Haemophilus influenzae* | 15 (4) | 2 (4) | 13 (4) | 1.000 |
| *Mycoplasma pneumoniae* | 11 (3) | 4 (8) | 7 (2) | 0.041 |
| *Moraxella catarrhalis* | 4 (1) | 0 | 4 (1) | 1.000 |
| *Chlamydophila pneumoniae* | 2 (<1) | 0 | 2 (<1) | 1.000 |
| *Staphylococcus aureus* | 2 (<1) | 1 (2) | 1 (<1) | 0.248 |
| Gram negative bacilli[a] | 6 (2) | 0 | 6 (2) | 1.000 |
| *Legionella pneumophila* | 0 | 0 | 0 | – |
| Other bacteria | 9 (2) | 3 (6) | 6 (2) | 0.102 |
| Patients with bacteria[b] | 69 (19) | 16 (33) | 53 (17) | 0.010 |
| Virus | | | | |
| Rhinovirus | 37 (11) | 3 (6) | 34 (11) | 0.447 |
| Influenza A virus | 23 (7) | 2 (4) | 21 (7) | 0.752 |
| Respiratory syncytial virus | 15 (4) | 0 | 15 (5) | 0.236 |
| Influenza B virus | 12 (3) | 0 | 12 (4) | 0.379 |
| Human metapneumovirus | 6 (2) | 1 (2) | 5 (2) | 0.575 |
| Parainfluenza virus type 3 | 2 (<1) | 0 | 2 (<1) | 1.000 |
| Adenovirus | 0 | 0 | 0 | – |
| Patients with virus[c] | 89 (24) | 6 (13) | 83 (26) | 0.046 |
| Patients with any pathogen[d] | 145 (40) | 21 (44) | 124 (39) | 0.635 |

*Data are shown as numbers (%). [a]Gram negative rods other than* Haemophilus *species and* Legionella. *[b]More than one bacterium detected: three patients. [c]More than one virus detected: six patients. [d]Mixed bacterial and viral infection: 13 patients. LRTI = lower respiratory tract infection.*

### Radiographic findings

Forty-eight patients (13%) had a pneumonic infiltrate on the chest radiograph. Patients with pneumonia were older than those without pneumonia (median age 61 versus 48 years, *P*<0.001); there was no significant difference in the presence of all underlying disease, ability to care for self, or smoking habits. Chronic obstructive pulmonary disease and immunisation against influenza were more prevalent in the group of patients with pneumonia, but there was no difference when adjusted for age. Sputum production was more common in patients without pneumonia.

### Microbiological findings

Twenty-two patients (6%) had been treated with antibiotics within the preceding 8 days. Blood was cultured in all but one patient. Sputum for culture and PCR were obtained from 340 (93%) patients. The identified pathogens are shown in Table 3.

Four of the patients (all with pneumonia) had pneumococcal bacteraemia. Pneumococci were not isolated from sputum in any of these (one had no sputum available). Patients with mycoplasma infection were significantly younger than those without mycoplasma infection (median age 34 versus 50 years; *P*<0.001), whereas there was no significant age difference between patients with or without pneumococcal infection (median age 56 versus 49 years, *P* = 0.060). In the influenza season (January–April), influenza virus was found in 15% and RSV in 7% of the active participants.

### Predictors of radiographic pneumonia

Sensitivities, PPVs, and crude and adjusted ORs for the predictor variables are shown in Table 4. All predictor variables were strongly associated with radiographic pneumonia with crude ORs between 3 and 5. However, the PPVs of these parameters were low and equivalent to the GPs' clinical diagnoses of pneumonia.

In crude and adjusted analysis, CRP ≥20 mg/l and $SATO_2$ ≤95% had the strongest association with radiographic pneumonia. To analyse further the predictive capacity of these two variables in the daily clinical setting, sensitivity and PPV of the GPs' diagnosis of clinical pneumonia in combination with either CRP ≥20 mg/l or $SATO_2$ ≤95% were calculated. This was done in two different ways: either by defining the predictor variable as a clinical diagnosis and CRP ≥20 mg/l ($SATO_2$ ≤95%) or as a

**Table 4. Predictors of radiographic pneumonia.**

| | All patients (*n* = 364) *n* (%) | Pneumonia (*n* = 48) *n* (%) | Non-pneumonic LRTI (*n* = 316) *n* (%) | *P*-value | Sensitivity | Specificity | PPV | NPV | Crude OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|
| Vital signs | | | | | | | | | | |
| Heart rate ≥100 BPM | 43 (12) | 12 (25) | 31 (10) | 0.006 | 0.25 | 0.90 | 0.28 | 0.89 | 3.06 (1.45 to 6.49) | 1.93 (0.83 to 4.51) |
| Respiratory rate ≥22 breaths/min | 89 (24) | 24 (50) | 65 (21) | <0.001 | 0.50 | 0.79 | 0.27 | 0.91 | 3.86 (2.06 to 7.24) | 1.93 (0.94 to 3.99) |
| $SATO_2$ ≤95% | 86/357 (20) | 25 (52) | 61/309 (20) | <0.001 | 0.52 | 0.80 | 0.29 | 0.92 | 4.42 (2.35 to 8.31) | 2.87 (1.42 to 5.80) |
| Temperature ≥38°C | 47/354 (13) | 14/47 (30) | 33/307 (11) | 0.002 | 0.30 | 0.89 | 0.30 | 0.89 | 3.52 (1.71 to 7.25) | 1.61 (0.70 to 3.72) |
| Biochemical markers of inflammation | | | | | | | | | | |
| CRP ≥20 mg/l | 145/363 (40) | 35 (73) | 110/315 (35) | <0.001 | 0.73 | 0.65 | 0.24 | 0.94 | 5.02 (2.59 to 9.88) | 2.83 (1.33 to 6.04) |
| Leukocyte count ≥10 million/ml | 86/362 (24) | 22 (46) | 64/314 (20) | <0.001 | 0.46 | 0.80 | 0.26 | 0.91 | 3.31 (1.76 to 6.21) | 1.33 (0.62 to 2.82) |
| GP's diagnosis | | | | | | | | | | |
| Clinical pneumonia | 122/345 (35) | 28 /47 (60) | 94 /298 (32) | <0.001 | 0.60 | 0.68 | 0.23 | 0.91 | 3.20 (1.70 to 6.02) | |
| Clinical pneumonia & CRP ≥20 mg/l | 71/344 (21) | 23/47 (49) | 48/297 (16) | <0.001 | 0.49 | 0.84 | 0.32 | 0.91 | 4.97 (2.60 to 9.52) | |
| Clinical pneumonia & $SATO_2$ ≤95% | 38/338 (11) | 15/47 (32) | 23/291 (8) | <0.001 | 0.32 | 0.92 | 0.39 | 0.89 | 5.46 (2.59 to 11.52) | |
| Clinical pneumonia or CRP ≥20 mg/l | 192/344 (56) | 39/47 (83) | 153/297 (52) | <0.001 | 0.83 | 0.48 | 0.20 | 0.95 | 4.59 (2.07 to 10.15) | |
| Clinical pneumonia or $SATO_2$ ≤95% | 164/338 (49) | 37/47 (79) | 127/291 (44) | <0.001 | 0.79 | 0.56 | 0.23 | 0.94 | 4.78 (2.29 to 9.97) | |

*PPV = positive predictive value. NPV = negative predictive value. CRP = C-reactive protein. OR = odds ratio.*

clinical diagnosis or a CRP ≥20 mg/l ($SATO_2$ ≤95%; Table 4). Addition of either of these values increased the PPV, but at the expense of a lower sensitivity. In the actual study, it means that GPs would have missed the diagnosis of pneumonia in five more patients (11%) by adding CRP ≥20 mg/l as a diagnostic criterion, and in 13 more patients (28%) by adding $SATO_2$ ≤95%. When the predictor variable was defined as a clinical diagnosis or CRP ≥20 mg/l, there was a high sensitivity (0.83), but a low PPV (0.20) due to a considerably higher rate of false-positive test results.

### Outcome

Information on hospital admittances and deaths were available for all patients. The Karnofsky performance status score at day 28 was available for 354 (97%) patients.

No patients died during the 4-week follow-up period. Nineteen patients (5%) were non-electively admitted to hospital. Thirteen of these patients were admitted within 2 days of enrolment. The risk of hospitalisation was higher for patients with pneumonia than for patients without pneumonia (19% versus 3%; $P<0.001$). This difference was still statistical significant when adjusted for age, underlying disease, and functional status. Of the 19 patients who were admitted to hospital, 10 had no pathogen detected and six had pneumococcal infection (including all of the four patients with bacteraemia). None of the patients with mycoplasma infection was hospitalised. At day 28, 89 patients (25%) had not reached their usual functional status, having a lower Karnofsky performance status score than before the development of the episode of LRTI. This was more common in patients with pneumonia than in non-pneumonic patients (43% versus 22%, $P = 0.006$).

## DISCUSSION

### Summary of main findings

In this prospective study of LRTI in a Danish primary care setting, possible aetiological pathogens were detected in 40% of the patients. Bacteria and viral infection were found equally often. Pathogens most frequently detected were rhinovirus (11%), influenza A virus (7%), and *S. pneumoniae* (6%). Bacteria were found more frequently in patients with pneumonia than in the non-pneumonic patients. Patients with pneumonia had a higher risk of admittance to hospital, and *S. pneumoniae* was the main pathogen detected in these cases. Patients with pneumonia seem to recover more slowly than those who do not have pneumonia. Vital signs and simple biochemical markers of inflammation have a strong association with radiographic pneumonia in patients diagnosed with LRTI by GPs, but the PPVs of these variables are low.

### Strengths and limitations of the study

The study population included patients diagnosed with LRTI and treated accordingly in general practice. As in everyday practice, some of the patients may have had other respiratory or infectious illnesses mimicking LRTI. Mirroring this routine situation, this study design makes the results widely applicable in daily practice.

Of the study patients, only approximately half were included as active participants. The fact that non-participants were comparable in baseline measures excludes major selection bias. The difference in antibiotic prescribing, it can be assumed, is explained by the GPs withholding decision of treatment until results from microbiology and radiography were available for the active participants. Radiographic pneumonia was used as an indicator of necessity of antibiotic treatment, although some cases are viral in origin and some bacterial cases resolve without treatment. Interpretation of chest radiographs is subjected to inter-observer variability,[14–16] and high-resolution computed tomography reveals pneumonic changes in about 50% more patients with LRTI than conventional radiography.[17] However, radiographically-verified pneumonia is still a potentially severe infection and, as the data show, the most severely ill patients are found in the group with pneumonia. Moreover, conventional radiography is the reference standard for defining pneumonia in international guidelines. An alternative method is to use bacterial aetiology,[18] but sputum culture from healthy adults may grow bacteria without any clinical relevance. No excellent gold standard for 'LRTI requiring antibiotics' exists.[19] Chest radiography in the research setting was used but it should not to be recommended in all cases of LRTI in daily practice in primary care.

The epidemic and cyclic character of some pathogens greatly influences prevalence measures. National surveillance records support that the exclusion of November, December, and the summer months was unlikely to have had a significant impact on the proportion of the various pathogens detected. Ideally, there should be more than 1 year of enrolment.

The use of hospitalisation as an outcome measure can be questioned. GPs' thresholds for referral to hospital vary, and social status may influence the patients' ability to cope at home. However, the association between pneumonia and hospitalisation was still statistically significant when adjusted for age, underlying disease, and functional status prior to the episode of LRTI. This was also true for the association between pneumococcal aetiology and hospitalisation. This supports the assumption that pneumonia and pneumococcal aetiology were associated with hospitalisation regardless of age and

disabilities. Moreover, the patients were referred to the same local hospital, ruling out major differences in the threshold for acceptance of admittance by the hospital. GPs' knowledge of positive blood culture results or presence of radiographic infiltrates may have influenced their decision to admit patients to hospital. Median length of hospital stay was 6 days: 10 days for pneumonic patients compared with 2 days for patients without pneumonia, indicating that most referrals to hospital were well justified, and would have been the result even if the patients had not participated in the study.

### Comparison with existing literature

The lack of a gold standard for the diagnosis of LRTI or pneumonia in general practice, as well as differences in microbiological methods, contribute to differences in results between studies. The proportion of 13% pneumonic patients in this study corresponds to the 11 to 20% reported in studies with fairly similar inclusion criteria.[1,20–23] In a UK study of patients without any comorbid conditions, pneumonia was verified in only 6%,[24] and in studies of patients with a clinical diagnosis of pneumonia, the diagnosis could be verified in less than half of the patients.[25,26]

*S. pneumoniae* is relatively consistently isolated by sputum culture in 6–8% of patients with LRTI, but by use of additional microbiological analyses (detection of pneumococcal antigens in sputum or urine or PCR on airway secretions), pneumococci are found in up to 35%.[1,25,27] Detection of *Mycoplasma pneumoniae* is strongly influenced by its periodic occurrence and the age distribution of the population. In the population studied this pathogen was more frequently found in pneumonic compared with non-pneumonic patients, but the negative association with subsequent hospitalisation indicates that infection with this pathogen has a milder course compared with pneumococcal infection. Viral aetiology is reported in up to 63% of patients, much depending on microbiological methods applied.[27] In the present study, virus was detected in 24% of patients: 13% of pneumonic and 26% of non-pneumonic cases of LRTI. The more recently discovered HMPV, which was initially detected in children,[28] was detected in six patients.

The discrepancy between clinical and radiographic pneumonia is emphasised in this study. The PPV of the GPs' diagnosis of radiographic pneumonia was only 0.23, which is in accordance with other studies.[29–31] Forty per cent of the patients with radiographic pneumonia were not identified by the GPs. As found previously in other studies, symptoms and signs were unable to discern between pneumonic and non-pneumonic LRTI,[10] and elevated temperature,[30,32] CRP,[33,34] respiratory rate, and heart rate[35] were associated with pneumonia. Use of pulse oximetry only performed slightly better than respiratory rate in predicting pneumonia.

The best predictor of pneumonia was CRP. A cut-off point of 20 mg/l was chosen to evaluate the predictive value of CRP, as a relatively low value is required to achieve an acceptable sensitivity in predicting pneumonia in primary care.[32,33,36] In this setting, CRP ≥20 mg/l had a higher sensitivity than the GPs' clinical diagnosis, but specificities and predictive values were comparable. In daily practice, the interpretation of a CRP value is made in the context of clinical judgement, but combining the clinical diagnosis with the value of CRP did not perform convincingly in predicting radiographic pneumonia. The predictor 'clinical pneumonia OR CRP ≥20 mg/l', which has a high negative predictive value of 95%, would miss 17% of pneumonic cases, and illustrates the drawback of a strong negative predictor in a setting with few cases. Overall, the data do not support the use of CRP for the diagnosis of pneumonia in primary care. This is in accordance with a review on the diagnostic value of CRP in LRTI which leads to the conclusion that the sensitivity and the specificity of CRP in predicting pneumonia is too low, and that the use of CRP as a guide to antibiotic prescribing is not supported by current evidence.[37] The study does not alter this conclusion.

### Implications for future research and clinical practice

*S. pneumoniae* was the predominant bacterial pathogen, and was associated with the subsequent risk of hospitalisation. It is therefore highly important to choose an agent with activity against pneumococci in case antibiotic treatment is initiated for LRTI in primary care. In Denmark, penicillin and macrolide resistance in pneumococci is below 5%, and penicillin is still first choice of treatment of LRTI. As the accuracy of CRP in discriminating between bacterial and viral infections in primary care has been shown to be rather poor,[38] and the data do not support the introduction of CRP for the purpose of diagnosing pneumonia, CRP point-of-care tests should not be recommended in LRTI in this setting until the clinical value is investigated in prospective, controlled intervention trials using CRP-guided treatment algorithms.

Finally, it is worth mentioning that five of the 369 patients with an initial diagnosis of LRTI were shown to have pulmonary malignancy. It is important to be aware that malignancy may present with vague symptoms resembling LRTI, and in high-risk individuals (current or ex-smokers of more than 50 years of age), radiography of the lungs should be considered.

## Supplementary information

Additional information accompanies this paper at http://www.rcgp.org.uk/bjgp-suppinfo

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## Ethics committee

The study was approved by the Medical Ethics Committee of Funen and Vejle Counties (no. 20000008)

## Competing interests

The authors have stated that there are none

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