Community acquired pneumonia—a prospective UK study

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Abstract

***Background*—There are few data on paediatric community acquired pneumonia (PCAP) in the UK.**

***Aims*—To investigate the aetiology and most useful diagnostic tests for PCAP in the north east of England.**

***Methods*—A prospective study of hospital admissions with a diagnosis of PCAP.**

***Results*—A pathogen was isolated from 60% (81/136) of cases, and considered a definite or probable cause of their pneumonia in 51% (70/136). Fifty (37%) had a virus implicated (65% respiratory syncytial virus) and 19 (14%) a bacterium (7% group A streptococcus, 4% *Streptococcus pneumoniae*), with one mixed infection. Of a subgroup (51 patients) in whom serum antipneumolysin antibody testing was performed, 6% had evidence of pneumococcal infection, and all were under 2 years old. The best diagnostic yield was from paired serology (34%, 31/87), followed by viral immunofluorescence (33%, 32/98).**

***Conclusion*—Viral infection accounted for 71% of the cases diagnosed. Group A streptococcus was the most common bacterial infective agent, with a low incidence of both *Mycoplasma pneumoniae* and *S pneumoniae*. Pneumococcal pneumonia was the most common bacterial cause of pneumonia in children under 2 years but not in older children. Inflammatory markers and chest *x* ray features did not differentiate viral from bacterial pneumonia; serology and viral immunofluorescence were the most useful diagnostic tests.**

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Community acquired pneumonia in childhood remains a major cause of morbidity worldwide and a significant cause of death in developing countries.[1] In the UK it is still a common reason for hospital admission. Rational treatment of pneumonia depends on knowing the most likely pathogens in each community, as the relative frequency of different agents varies from one geographical region to another.

Most cases are treated empirically without a causative agent being isolated, in part because even in a major centre the approach to the investigation of paediatric community acquired pneumonia (PCAP) is inconsistent with a diagnostic yield of only about 50%.[2] There have been many studies of adult and paediatric community acquired pneumonia (CAP) elsewhere in Europe,[3–6] and multicentre UK studies of pneumonia in adults have lead to recommendations for investigation and treatment.[7] In contrast, there are few data for children in the UK, and reliable methods for identifying a causative agent are lacking. Blood cultures have a low sensitivity, lung taps are considered too invasive for routine diagnostic use, while non-culture techniques are not widely used. Antibiotic use in the community and difficulty in obtaining sputum samples from young children hinder culture, while upper respiratory tract carriage of bacteria makes it difficult to assess the significance of nose, throat, and nasopharyngeal secretion cultures.

In the light of the paucity of UK PCAP data, this prospective study sought to establish the causes of PCAP and to identify the most useful investigations.

Patients and methods

PATIENTS

All patients (0–16 years) admitted to Newcastle General Hospital's (NGH) Paediatric Unit with a diagnosis of CAP, between 1 November 1996 and 1 June 1998 were studied. This unit offers paediatric intensive care and an infectious diseases service for secondary and tertiary referrals. Ethical approval and fully informed parental consent was obtained.

Pneumonia was defined as acute respiratory symptoms (tachypnoea, respiratory distress, fever, cough, lethargy, wheeze) with compatible chest *x* ray findings (infiltration, collapse, consolidation, perihilar, and peribronchial changes). Patients with known immunodeficiency or who had been inpatients in the previous three weeks were excluded.

A total of 136 cases aged 2 weeks to 16 years (mean 35.4 months) were enrolled; 14 were tertiary referrals. Seventy (51%) were less than 2 years old; 79 (58%) were male, 57 female, and 94 (69%) completed follow up. Underlying diseases included cerebral palsy (n = 2), prematurity (n = 3), spinal muscular atrophy (n = 2), Duchene muscular dystrophy (n = 2), and Treacher–Collins syndrome (n = 1). Eleven were ventilated; none died.

SAMPLES

On admission blood was taken for full blood count (FBC), erythrocyte sedimentation rate (ESR), C reactive protein (CRP), and culture; acute serum was stored. Upper respiratory tract secretions were sent for bacteriological and virological studies. These included nasopharyngeal secretions (NPS) from children

under 2 years, sputum (where possible), and/or nose and throat swabs from older children, as well as bronchoalveolar lavage (BAL) or pleural fluid if obtained. Children were reviewed at four to six weeks when convalescent serum was taken for serology. Chest *x* rays were reported by consultant radiologists unaware of the microbiological/viral diagnosis, then separated into the following groups: lobar consolidation, patchy consolidation, increased perihilar and peribronchial markings, pneumonitis, or consolidation with effusion.

MICROBIOLOGICAL INVESTIGATIONS

The Regional Public Health Laboratory Service (PHLS) performed all the investigations. Because potentially pathogenic bacteria frequently colonise the nasopharynx of healthy children and serological responses cannot always be interpreted unequivocally, results were clarified as either the definite, probable, or possible cause of pneumonia, depending on where samples were obtained from and the test used (table 1). For example, cases were designated "probable" when sputum cultures were positive as these are suggestive in adults, but children have difficulty producing adequate sputum samples.

Immunofluoresence was performed on NPS using either rabbit absorbed polyclonal sera (made in the regional laboratory) or monoclonal antibodies (Dako conjugated mouse pools). Viral culture of NPS was performed if immunofluorescence was negative. Blood was cultured using an automated system (Bac T Alert). Where sufficient sample was left, serum, secretions, and urine were stored for additional pneumococcal studies. Development of antibodies to pneumolysin has been shown after infection with *Streptococcus pneumoniae*. Serum antibodies to recombinant pneumolysin were detected by in house enzyme linked immunososrbent assay (ELISA). Pneumococcal capsular polysaccharide (cps) antigens were assayed by countercurrent immunoelectrophoresis (CIE) in urine and sputum. Pneumolysin antigen in sputum or NPS was assayed by Western blot analysis using a monoclonal antibody,[8] and pneumolysin gene in sputum by single polymerase chain reaction (PCR) using a commercial primer set (Novocastra Laboratories Ltd, Newcastle-upon-Tyne).

Infections caused by both viruses and bacteria were designated mixed viral/bacterial infections, although where a definite viral infection was found with only probable or possible bacterial infection this was regarded as definite viral infection for analysis. Those caused by two viruses or two bacteria were classified as dual viral or dual bacterial infections.

Statistical analysis was carried out using the χ^2 and Student's *t* tests.

Results

There were no deaths and all children recovered without major complications.

Acute serum was taken from 122, a urine sample and both acute and convalescent serology from 87, acute serology only from 35, convalescent serology only from seven, and no serology samples were obtained from seven. Nasopharyngeal secretions or sputum were obtained from 98 patients, nose and throat swabs from 65. Both NPS (or sputum) and swabs were taken in 48, neither in 21.

At least one pathogen was isolated from 81 children (60%). This was a virus in 52 (38%), and a bacterium in 28 (21%); in one there was a mixed infection. The isolated pathogen was deemed to be a definite cause of PCAP in 68 (50%; 50 viral, 17 bacterial, one mixed), a probable cause in two (bacterial), and a possible cause in 11 (nine bacterial, two viral).

A total of 104 pathogens were isolated of which 70 were considered to be the definite cause of the pneumonia, four the probable cause, and 30 the possible cause (table 2).

In 62 patients one pathogen was identified; in 15, two were found, and in four cases three pathogens were found. Of the 19 cases with more than one isolate, a virus and bacterium were found in 15, 14 of which had a definite viral isolate plus a possible bacterium and so were defined as a "definite viral" pneumonia; one had both a definite viral and a definite bacterium, defined as "mixed". The other four included one with a dual viral infection and

Table 1 Microbiological investigations and diagnostic criteria

Specimen	*Agent/antigen*	*Assay*	*Diagnostic criteria*		
			Definite	*Probable*	*Possible*
Serum	Respiratory viruses/antibodies	CF	Acute titre ⩾1/128 or a fourfold rise	Convalescent titre ⩾1/128	—
	Coxiella burnetti/antibodies	CF	Acute titre ⩾1/128 or a fourfold rise	Convalescent titre ⩾1/128	—
	Mycoplasma pneumoniae/antibodies	CF	Acute titre ⩾1/128 or a fourfold rise	Convalescent titre ⩾1/128	—
	Cytomegalovirus	CF	Acute titre ⩾1/128 or a fourfold rise	Convalescent titre ⩾1/128	—
	Chlamydia psittaci	CF	Acute titre ⩾1/128 or a fourfold rise	Convalescent titre ⩾1/128	—
	Group A streptococcus	ASOT	>2 dilutional increments	—	—
	S pneumoniae/antipneumolysin antibodies	ELISA	Twofold rise in titre	—	—
	Cold agglutinins		⩾1:32	—	—
	Bacteria	Culture	Growth	—	—
NPS/sputum	Respiratory viruses	IF	Positive	—	—
	Bacteria	Culture	—	Growth	—
	S pneumoniae/CPS	CIE	—	Positive	—
	Pneumolysin antigen	Western blot	—	Positive	—
	Pneumolysin gene	PCR	—	—	Positive
N/Tswabs	Respiratory viruses	Culture	Growth	—	—
	Bacteria	Culture	—	—	Growth
Urine	*S pneumoniae*	CIE	Positive	—	—

Respiratory viruses tested were: RSV, influenza A+B, parainfluenza 1, 2, and 3 virus, and adenovirus.
ASOT, antistreptolysin O titre; ELISA, enzyme linked immunosorbent assay; IF, immunofluorescence; CPS, capsular polysaccharide antigen; CIE, countercurrent immunoelectrophoresis; PCR, polymerase chain reaction; CF, complement fixation.

Table 2 Pathogens isolated from cases with pneumonia

	Definite and probable n (%)	*Possible n (%)*
Bacteria		
Group A streptococcus	9 (7)	0
Mycoplasma pneumoniae	3 (2)	0
Streptococcus pneumoniae	5 (4)	18 (13)
Bordatella pertussis	1 (0.7)	0
Chlamydia trachomatis	1 (0.7)	0
Pseudomonas	1 (0.7)	0
Staphylococcus aureus	0	1 (0.7)
Moraxella sp.	1 (0.7)	1 (0.7)
Haemolytic streptococci (not group A)	0	1 (0.7)
Haemophilus influenzae	1 (0.7)	7 (5)
Viruses		
RSV	34 (25)	0
Influenza A	7 (5)	0
CMV	4 (3)	0
Adenovirus	2 (1.4)	0
Varicella	1 (0.7)	0
Parainfluenza	1 (0.7)	0
Rhinovirus	1 (0.7)	0
Coxsackie	1 (0.7)	0
EBV	1 (0.7)	0
HSV-1		1 (0.7)
Enterovirus		1 (0.7)

n, number of cases; %, percentage of total cases.

S pneumoniae identified on polymerase chain reaction (PCR), and three with dual bacterial infection.

Paired serology gave the best diagnostic yield at 34% (31/87), followed by viral immunofluorescence at 33% (32/98). Sputum culture was positive in five, bacterial culture of nose or throat swabs in 16, and viral culture of NPS in two. Only one of the 110 blood cultures was positive (group A streptococcus).

From the pneumococcal studies, 3/51 cases (6%) showed a significant rise in antibody to pneumolysin; 14/31 (45%) were positive for pneumolysin by polymerase chain reaction (SPN PCR) on respiratory secretions. None were positive for pneumococcal antigen by capsular polysaccharide CIE in secretions or urine, or for pneumolysin antigen by Western blot in secretions.

VIRAL INFECTION

Viral infection was the most common cause of pneumonia, a virus being isolated from 53 (39%); 50 had a definite infection, two a possible infection, and one a mixed infection. Respiratory syncytial virus (RSV) was the most frequent, being identified in 34 (25%). Nineteen babies had clinical features of bronchiolitis (mean age 2.7 months) but the other 15 cases of RSV infection were in older children with a clinical diagnosis of pneumonia (mean age 33.3 months). Seven of these were diagnosed by serology, six by immunofluorescence, one by nose/throat swab culture, and one by both immunofluorescence and serology.

Other viral causes of pneumonia included influenza A (n = 7; four from immunofluorescence, three from serology), cytomegalovirus (CMV; n = 4, all diagnosed from serology), and adenovirus in two (one by immunofluorescence, one cultured on nose/throat swab). There was one viral coinfection (adenovirus on immunofluorescence with CMV on serology) and one mixed infection with both influenza A and group A streptococcus. Two viruses isolated from nose/throat swab culture were considered possible causes of pneumonia: herpes simplex type 1 and an enterovirus.

BACTERIAL INFECTION

Bacteria were found in 43 children (32%), but in 14 were cultured only on nose or throat swab, making their significance uncertain; hence bacteria were causally implicated in 29 children (21%). Of these 17 (12.5%) were considered to represent definite infection, two probable, nine possible, and one mixed.

Group A streptococcal infection was the most common definite diagnosis, found in 9/136 (7%), with eight cases diagnosed by a raised antistreptolysin O titre (ASOT) and one by blood culture together with an increased ASOT and anti-DNAse antibody. Three children with group A streptococcal infection had pleural effusions. *S pneumoniae* was a definite or probable pathogen in 5/136 (4%) of the total, being isolated from CSF in one baby with pneumococcal meningitis and an acute pneumonia, by a rise in antipneumolysin antibody in three, and from sputum in one patient who also had influenza A infection. Paired pneumolysin antibody testing was achieved in 51; of these, 6% (3/51) were positive (all ⩽2 years old), whereas only 30% (16/51) of those tested were ⩽2 years old.

Mycoplasma pneumoniae was found by serology in three (2%) and cold agglutinins were positive in two of these. *Bordatella pertussis* was isolated from a pernasal swab in one baby and *Chlamydia trachomatis* from NPS culture in a 4 week old baby with pneumonitis.

S pneumoniae was the most frequently isolated bacterium (17%), but in most cases (18/23) was only a possible causative pathogen, being found in secretions either by pneumolysin PCR (n = 14) and/or culture (n = 6). RSV was also found in eight of these cases and other viruses in four, leaving six children in whom *S pneumoniae* was classified as a possible pathogen.

There were 16 positive nose/throat swab cultures from which four species of bacteria were isolated (*S pneumoniae* in eight, *Haemophilus influenzae* in six, haemolytic streptococci (not group A) in one, and *Moraxella catarrhalis* in one). There were 14 positive pneumolysin PCRs, two of which also had positive swab results.

There were no definite cases of bacterial coinfection, but in one case *S pneumoniae* was isolated on a throat swab in a child with an increased ASOT, and *Moraxella catarrhalis* was isolated on a swab in a child who had a rising titre to *Mycoplasma pneumoniae*.

LABORATORY INVESTIGATIONS

There were no significant differences in the total white cell count, neutrophil count, ESR, and CRP between different diagnostic groups (table 3).

RADIOGRAPHIC APPEARANCE

The different radiographic appearances were categorised into five groups (see table 4). There

Table 3 Results of laboratory investigations

Diagnostic group	Mean WCC ($\times 10^9$/l) (range)	Mean neutrophil count ($\times 10^9$/l) (range)	Mean ESR (mm/h) (range)	Mean CRP (mg/l) (range)
Bacterial alone (definite + possible)	18.00 (n = 25) (5–36.5)	13.5 (n = 19) (2.5–32)	48.8 (n = 18) (5–120)	100 (n = 19) (7–365)
Viral alone (definite)	13.03 (n = 35) (4–35)	9.4 (n = 29) (1.5–31)	36.4 (n = 11) (5–90)	79 (n = 18) (4–327)
	p = 0.042	p = 0.11	p = 0.32	p = 0.64

WCC, white cell count; ESR, erythrocyte sedimentation rate; CRP, C reactive protein.

Table 4 Chest x ray categories of pneumonia cases

x ray	Viral	Bacterial (definite)	Bacterial (probable)	Bacterial (possible)	Viral (possible)	Chlamydia	Mixed	Unknown
Lobar	1	1		1	1		2	4
PC	18	8	4	4			10	39
Increased PH + PB markings	14	1		2			7	11
Pneumonitis						1		
Effusion	1	3		2	1			

PC, patchy consolidation; PH, perihilar; PB, peribronchial.

was no significant difference between any of the groups.

Discussion

A definite causative agent was found in 50% of children with pneumonia, similar to results from elsewhere in Europe.[3 9 10] In two thirds this was a virus, a higher proportion than in previous studies[5 6 11–13]; bacterial causes (12.5%) were less common. In some studies, where bacterial antibody assays and antigen detection were used in addition to conventional methods,[3 4] a causative agent was found in up to 70% of cases, of which 40–50% were bacterial. In our study a possible causative agent was found in a further 10%, reflecting bacteria isolated from nose or throat swabs by culture or PCR. However, these probably represent nasopharyngeal carriage as 45% of swabs taken (29/65) were positive. Most were *S pneumoniae* and while it is possible that they may have been pathogenic, in most cases a virus was detected; in only six were pneumococci found in isolation.

Viral diagnoses were made in 37% of the children, with RSV detected most frequently. Not only was it the major pathogen in infantile bronchiolitis, but it also caused classical pneumonia in older children, a finding not always appreciated. Influenza A and adenovirus are well recognised respiratory pathogens and together were responsible for 5% of cases. CMV and EBV rarely cause pneumonia in immunocompetent children but have been previously reported to do so.[14 15] It is more questionable as to whether the HSV-1 and enterovirus isolated caused pneumonia.

Group A streptococcus was the most frequently detected bacterium from the definite group, accounting for nine cases (7%). We have noted this previously,[2] but it is not well reported in other studies, as it is seldom tested for. Importantly three of the nine children with group A streptococcal pneumonia were seriously unwell with pleural effusions (n = 3) and septicaemia (n = 1).

In this study mycoplasma was found in only three (2%) and *S pneumoniae* in five (4%), whereas mycoplasma infections accounted for 7–40% of cases and pneumococcal infection for 15–28% in other studies.[4 6 11 12]

Of those with pneumococcal infection, two (1.5%) of the diagnoses were made by culture, and three (2.5%) by a rise in antipneumolysin antibody. However, antipneumolysin antibody testing was performed in only 38% and the yield from those tested was 6%, suggesting 7.5% may have had pneumococcal pneumonia. This is in keeping with the only other study from the UK using non-culture techniques which found pneumococcus in 8% by blood PCR.[10] Antibody assays to identify bacteria such as *S pneumoniae*, *H influenzae* (non-capsulated), *Moraxella catarrhalis*, *Chlamydia pneumoniae*, *C trachomatis*, and *Mycoplasma pneumoniae* have been used in the most recent studies from the USA[11] and Finland.[12] They appear to be specific but may lack sensitivity, especially as children aged less than 2 years mount a poor humoral response to polysaccharide antigens.[16] Studies combining antibody and antigen detection to increase sensitivity suggest pneumococcal pneumonia is more common in younger children.[3 5 11] This study population was also young with 51% under 2 years, and although 70% of those tested for antipneumolysin antibody were over 2 years, all the positives were for those aged 2 years or under. So for those under 2 years old, 3/16 (19%) of those tested, had evidence of pneumococcal infection. This suggests for this population pneumococcus may well be the most frequent bacterial cause of pneumonia in children less than 2 years old, accounting for perhaps a fifth of cases of pneumonia in this age group; it does not, however, contribute significantly to childhood pneumonia in older children.

Curiously, an epidemiological UK study[17] suggested that 44% of childhood pneumonias were pneumococcal, and 75% may be. The diagnosis of pneumococcal pneumonia was based only on radiological appearances, together with white cell count greater than 15×10^9/l or CRP greater than 8 mg/l, but no microbiological data. As neither *x* ray appearance, white cell count, ESR, or CRP can reliably distinguish viral from bacterial pneumonia,[18–20] nor was any significant difference seen in the present study between viral and bacterial groups for pattern of radio-

graphic changes, white cell count, neutrophils, ESR, or CRP, these data seem most unreliable. CRP may be the most useful marker of bacterial infection with concentrations above 40 mg/l suggesting bacterial involvement,[21] although viral infections such as adenovirus can also induce high CRP.[22 23]

The two most useful investigations were immunofluorescence and serology, RSV being isolated by immunofluorescence in all cases of bronchiolitis, but in only 50% of RSV pneumonias, mainly because suitable samples were not obtained. Generally NPS are not taken from older children because this is considered an unpleasant procedure; but had more been performed a more rapid viral diagnosis could have been made, potentially allowing antibiotic prescribing to be rationalised.

Blood cultures were positive in only one case, confirming previous reports of their low yield, which may be because of low sensitivity, preadmission antibiotic treatment, or simply a low incidence of bacterial PCAP in the UK compared to tropical countries.[24]

Non-culture rapid diagnostic techniques should increase the diagnostic rate in PCAP. PCR techniques allow detection of *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*,[11 13] and *Bordetella pertussis* in sputum, and *Streptococcus pneumoniae* in blood.[13] However, healthy controls may be serum PCR positive, presumably related to pneumococcal carriage.[25]

This is the first study confirming the role of *S pneumoniae* in pneumonia in very young children in the UK, where it accounts for one fifth of cases. This is perhaps unsurprising as *S pneumoniae* more commonly invades sterile sites to cause septicaemia and meningitis in young children who are less able to mount an effective antibody response than older children. In older children pneumococcal pneumonia is much less common and in this group viruses, particularly RSV, are much more important. Mixed and dual infections are unusual except in association with RSV, highlighting the risk of bacterial superinfection in infants with RSV.

Bacteria are uncommonly detected as causes of PCAP in the UK, at least when using standard techniques. Viruses are much more common causes and viral immunofluorescence studies on sputum together with acute and convalescent serology greatly increase the diagnostic yield. Newer PCR methods for the detection of both bacteria and viruses should increase the yield still further. The role of bacteria, especially *S pneumoniae*, in PCAP in the UK must be examined more closely by using bacterial antibody detection and PCR to rationalise antibiotic prescribing and assess the cost effectiveness of a pneumococcal vaccine.

1 Chreten J, Holland W, Macklem P, Marray J, Woolcock A. Acute respiratory infections in children. A global public health problem. *N Engl J Med* 1984;**310**:982–4.
2 Dodman T, Clark.J, Cant AJ. Community acquired pneumonia: investigations, aetiology, treatment and outcome. *Eur J Pediatr* 1999;**158**:1005.
3 Korppi M, Heiskanen-Kosma T, Jalonen E, *et al*. Aetiology of community-acquired pneumonia in children treated in hospital. *Eur J Paediatr* 1993;**152**:24–30.
4 Nohynek H, Eskola J, Laine E, *et al*. The causes of hospital-treated acute lower respiratory tract infection in children. *Am J Dis Child* 1991;**145**:618–22.
5 Claesson BA, Trollfors B, Brolin I, *et al*. Etiology of community-acquired pneumonia in children based on antibody responses to bacterial and viral antigens. *Paediatr Infect Dis J* 1989;**8**:856–62.
6 Ausina V, Coll P, Sambeat M, *et al*. Prospective study on the etiology of community-acquired pneumonia in children and adults in Spain. *Eur J Clin Microbiol Infect Dis* 1988;**7**: 343–7.
7 British Thoracic Society Research Committee. Community-acquired pneumonia in adults in British hospitals in 1982–1983: a survey of aetiology, mortality, prognostic factors and outcome. *QJM* 1987;**239**:195–220.
8 Wheeler J, Freeman R, Steward M, *et al.* Detection of pneumolysin in sputum. *Diagn Microbiol* 1999;**48**:863–6.
9 Isaacs D. Problems in determining the etiology of community-acquired childhood pneumonia. *Paediatr Infect Dis J* 1989;**8**:143–8.
10 Shears P, Wright A. Community-acquired infections among children in an urban environment: a 2-year prospective study in Liverpool, UK. *J Infect* 1995;**30**:173–7.
11 Wubbel L, Muniz L, Ahmed A, *et al*. Etiology and treatment of community-acquired pneumonia in ambulatory children. *Paediatr Infect Dis J* 1999;**18**:98–104.
12 Heiskanen-Kosma T, Korppi M, Jokinen C, *et al*. Etiology of childhood pneumonia: serologic results of a prospective, population-based study. *Paediatr Infect Dis J* 1998;**17**:986–91.
13 Clements H, Stephenson T, Gabriel V, *et al*. Aetiology of community acquired pneumonia. A prospective study. Proceedings of the Royal College of Paediatrics and Child Health Annual Spring Meeting. *Arch Dis Child* 1998;**78**:28.
14 Smith SD, Cho CT, Brahmacupta N, Lenahen MF. Pulmonary involvement with cytomegalovirus infections in children. *Arch Dis Child* 1977;**52**:441–6.
15 Andiman WA, Markowitz RI, Hartsmann DM. Clinical, virologic, and serelogic evidence of Epstein-Barr virus infections in association with childhood pneumonia. *J Pediatr* 1981;**99**:880–6.
16 Koskela M. Serum antibodies to pneumococcal c-polysaccharide in children: a response to acute pneumococcal otitis media or to vaccination. *Paediatr Infect Dis J* 1987;**6**:519–26.
17 Djuretic T, Ryan MJ, Miller E, *et al*. Hospital admissions in children due to pneumococcal pneumonia in England. *J Infect* 1998;**37**:54–8.
18 Nohynek H, Valkeila E, Leinonen M, Eskola J. Erythrocyte sedimentation rate, white cell count and serum C-reactive protein in assessing etiologic diagnosis of acute lower respiratory infections in children. *Paediatr Infect Dis J* 1995;**14**: 484–90.
19 McCarthy PL, Frank AL, Ablow RC, *et al*. Value of the C-reactive protein test in the differentiation of bacterial and viral pneumonia. *J Pediatr* 1978;**92**:454–6.
20 Turner RB, Lande AE, Chase P, *et al*. Pneumonia in pediatric outpatients: cause and clinical manifestations. *J Paediatr* 1987;**111**:194–200.
21 Putto A, Ruuskanen O, Meurman O, *et al.* C-reactive protein in the evaluation of febrile illness. *Arch Dis Child* 1986;**61**:24–9.
22 Korpii M, Kroger L. C-reactive protein in viral and bacterial respiratory infection in children. *Scand J Infect Dis* 1992;**25**:207–13.
23 Ruuskanen O, Putto A, Sarkkinen H, *et al.* C-reactive protein in respiratory virus infections. *J Pediatr* 1985;**107**: 97–100.
24 Silverman M, Stratton D, Diallo A, Egler LJ. Diagnosis of acute bacterial pneumonia in Nigerian children. *Arch Dis Child* 1977;**52**:925–31.
25 Dagan R, Shriker O, Hazan I, *et al*. Prospective study to determine clinical relevance of detection of pneumococcal DNA in sera of children by PCR. *J Clin Microbiol* 1998;**36**: 669–73.