IMPROVING OUTCOMES IN PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA

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Abstract

Community-acquired pneumonia (CAP) is a leading cause of adult morbidity and mortality worldwide despite decades of effective antibiotics and vaccination initiatives. There have been no recent significant improvements in outcomes, including 30-day mortality. The bacterium *Streptococcus pneumoniae* is the most prevalent causative pathogen in CAP, being found in up to half of cases. In September 2006 a childhood pneumococcal vaccine (PCV-7) was introduced, leading to reductions in vaccine-type (VT) pneumococcal disease in infants, with possible additional benefits reported in adults. However, the effect that infant PCV-7 vaccination has on adult disease has to date been inadequately described in a small fraction of patients with invasive CAP, almost exclusively in populations in the US. These issues are explored fully in the literature review, encompassing chapters 1, 2 and 3.

New strategies for CAP are therefore required. The outcome of CAP can be improved by a) preventing the disease by vaccination and herd immunity, and b) ameliorating the course of the disease after it has been acquired. This thesis presents a collection of studies that aim to acquire observational data to investigate these two issues.

The majority of the included studies are drawn from a two year prospective cohort study of consecutive adults with CAP admitted to a large UK teaching hospital trust between September 2008 and September 2010. After obtaining informed consent, the presence of pneumococcal disease in each participant was established by testing urine samples for pneumococcal capsular polysaccharide, a test which has a high sensitivity and specificity. The urine samples were subsequently tested for pneumococcal serotype. A full record of care processes, investigations, and clinical outcomes was made, and child contact in the month preceding admission was assessed. These methods are described more fully in chapter 4.

Chapter 5 presents the data on the pneumococcal serotypes found in the cohort over a two year period, and links them to epidemiological characteristics in the study population. The most prevalent serotypes were 14, 1, 8, 3 and 19A, with VT serotypes less frequent in the second year of the study. Chapter 6 examines the association that infecting serotype has with disease manifestation and patient characteristics. Infection with a serotype not contained within PCV-7 (NVT) was associated with younger and fitter patients, a higher rate of complications such as para-pneumonic effusion, and hypotension at admission. The effect of child contact on pneumococcal disease is reported in chapter 7. Prior contact with a child aged ≤8 years was particularly associated with pneumococcal aetiology, and contact with a PCV-7 vaccinated child independently associated with NVT CAP. The findings from these three chapters are unique in that they relate individual pneumococcal serotype to specific clinical disease patterns, epidemiology and transmission in both invasive and non-invasive pneumococcal CAP for the first time. They show a change in serotype distribution in adults following the introduction of PCV-7 in infants, which is important to inform future vaccine development for both adults and children. Furthermore, different serotypes are associated with different clinical disease patterns, which may have a significant impact on the disease that clinicians see at the “front door” given that the serotype distribution of pneumococcal CAP may be changing. Finally, the link between child vaccination and adult disease provides more direct evidence for the transmission of pneumococci from children to adults as a mechanism for the development of CAP in adults.

The second part of this thesis looks at current care processes, and how these might be improved. Chapters 8, 9 and 10 relate to efforts to better predict prognosis, and chapters 11 and 12 with how patents with CAP may be better managed at the “front door”. Symptoms are clearly important to patients, but the role of symptoms in management and outcome is unclear. Chapter 8 presents a study validating a symptom score that has not yet entered routine use, but which is shown to correlate with clinical outcomes, and may be useful in assessing outcome in low severity CAP.

The influence that oxygenation status at admission has on outcome is poorly understood. Chapter 9 describes a study showing that whilst hypoxaemia does positively predict adverse outcome, it is not as predictive as existing severity scores. The presence of hypoxaemia may however identify a subset of patients who are classified as low severity by existing severity scoring, but are nevertheless at increased risk of adverse outcome.

Severity scoring is the cornerstone of management in adult CAP, and is explored in chapter 10. Current severity scores adequately predict mortality in CAP, but often generate a group of “moderate severity” where appropriate management is often unclear. This study looked at the effect of pre-admission functional status on outcome in conjunction with existing severity scores in this difficult group, and validated a novel severity score for predicting need for escalation of care, SMART-COP. Incorporation of functional status does marginally improve the performance of existing severity scores, but may be of more use as a post-severity score test to identify sub-groups of patients with moderate severity CAP who are at increased risk of death.

Chapter 11 looks at the influence that making a prompt *diagnosis* (rather than prompt *treatment* with antibiotics, as has previously been studied) has on outcome, using the time between admission and first chest radiograph as a surrogate measure. Whilst an early chest radiograph was not associated with an improvement in mortality, it was associated with a shorter length of hospital stay, and may therefore be regarded as a marker of good quality care.

There is current debate as to the role of the speciality physician in the front-door early assessment of patients, and whether early review of patients with CAP may improve outcome compared with management by a non-specialty physician. Chapter 12 looks at the effect that early specialist senior respiratory review has on outcome for adults with CAP, showing a clear benefit on length of hospital stay to early consultant review.

In conclusion, this thesis provides an up-to-date picture of the circulating pneumococcal serotypes in non-invasive adult CAP, and correlates infecting serotype to clinical and epidemiological parameters. It also identifies five areas of clinical care where management processes could be improved. By addressing of these aspects the outcome of CAP may be improved in the future.

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Publications arising

Original research publications arising from this thesis are listed below:

"Serotype prevalence in adults hospitalised with pneumococcal non-invasive community-acquired pneumonia." Bewick T, Sheppard CL, Greenwood S et al. *Thorax accepted for publication* (2011).

"What is the role of pulse oximetry in the assessment of a patient with community-acquired pneumonia in primary care?" Bewick T, Greenwood S, Lim WS. *Prim Care Respir J* 19:378-382 (2010).

"The impact of an early chest radiograph on outcome in patients hospitalised with community-acquired pneumonia". Bewick T, Greenwood S, Lim WS. *Clinical Medicine* Vol 10, No 6: 563–7(2010).

"Does early review by a respiratory physician lead to a shorter length of stay for patients with non-severe community-acquired pneumonia?" Bewick T, Cooper VJ, Lim WS. *Thorax* 64:709-712 (2009).

Other publications connected with this thesis are listed below:

"Clinical and laboratory features distinguishing pandemic H1N1 influenza-related pneumonia from inter-pandemic community-acquired pneumonia". Bewick T, Myles P, Greenwood S et al. *Thorax* 66(3):247-252 (2011).

"Managing passengers with respiratory disease planning air travel: British Thoracic Society recommendations." British Thoracic Society Standards of Care Committee (contributor and member of working party). *Thorax, accepted for publication* (2011).

"CURB-65 Pneumonia Severity Assessment Adapted for Electronic Decision Support". Jones BE, Jones J, Bewick T et al. *Chest* (2010)

"Risk factors for hospitalisation and poor outcome with pandemic A/H1N1 influenza: United Kingdom first wave (May-September 2009)." Nguyen-Van-Tam JS, Openshaw PJM, Hashim A, et al. (Bewick T Collaborator) *Thorax* 65(7):645–651 (2010).

"Community-Acquired Pneumonia in Primary Care". Opinion sheet no.33 for the General Practice Airways Group (GPIAG). Bewick T, Lim WS. http://www.pcrs-uk.org/opinions/os33_pneumonia.pdf (2010).

"The diagnosis of community-acquired pneumonia in adults." Bewick T, Lim WS. *Exp Rev Resp Med* 3(2):153-164 (2009).

"Chapter 8: "Pneumococcal disease and vaccines." Bewick T, Lim WS. Lung Infections, Oxford University Press.

"10 points on the diagnosis and management of the complications of influenza." Bewick T, Lim WS. *Pulse*, 27th May (2009).

List of abbreviations

BTS	British Thoracic Society
CAP	Community-acquired pneumonia
CC	Critical care
CCI	Charlson Co-morbidity Index
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CVA	Cerebrovascular Accident
CXR	Chest X-ray
DBP	Diastolic Blood Pressure
GP	General Practitioner
HPA	Health Protection Agency
HR	Heart rate
LOS	Length Of hospital Stay
LRTI	Lower respiratory tract infection
IRVS	Intensive Respiratory or Vasopressor Support
NCH	Nottingham City Hospital
NPV	Negative Predictive Value
OM	Otitis Media
OR	Odds Ratio
QMC	Queen's Medical Centre
PPV	Positive Predictive Value
PSI	Pneumonia Severity Index
RSIL	Respiratory and Systemic Infection Laboratory
SBP	Systolic Blood Pressure
TFA	Time from admission to first antibiotic dose
TXR	Time from admission to first chest radiograph
UK	United Kingdom

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Chapter 1: The burden of community-acquired pneumonia

“It is much more important to know what sort of patient has a disease than what sort of disease a patient has.”

Sir William Osler

Introduction

As an introduction to this thesis, this chapter describes the current burden of community-acquired pneumonia (CAP) in the UK population and worldwide, with particular focus on *Streptococcus pneumoniae*.

Definition

CAP is defined by the British Thoracic Society (BTS) as "symptoms and signs consistent with an acute lower respiratory tract infection associated with new radiographic shadowing for which there is no other explanation (for example, not pulmonary oedema or infarction) where the illness is the primary reason for hospital admission and is managed as pneumonia".[1]

Epidemiology

Population incidence

A variety of studies have estimated the incidence of CAP within the general population. The most recent study analysed a primary care patient database (The Health Information Network; (THIN)) covering the years 1991 to 2003 for diagnoses of CAP recorded by general practitioners (GPs),[2] representing 56,332 cases in 4% of the UK population. The overall annual incidence of CAP in this cohort was 2.33/1000 population, with CAP being particularly common in those aged less than 5 years (1.91/1000 population per year) and more than 60 years (6.66/1000 population per year). CAP was more common amongst those of male sex and lower socioeconomic status. A similar study performed in another UK primary care database (QRESEARCH) included 34,098 cases of CAP, and calculated an overall incidence of 1.15/1000 patient-years.[3] Another study of comparable size was performed in Seattle, USA, where 15,141 cases of physician-defined CAP were identified over a twelve year period, giving a much higher annual incidence of 12/1000, rising to 34/1000 in those aged more than 75 years.[4] However, when data were presented in this study from a non-influenza pandemic year (1965), the incidence was substantially lower

across all age groups. A smaller Finnish study described a rate of 11.6/1000 amongst a smaller population of 46,979 in one calendar year.[5] These studies are necessarily limited in that the definition used for inclusion was physician reported diagnoses, many of which would not have had a confirmatory chest radiograph. A study involving a population of 74,368 in Barcelona, Spain, of radiographically confirmed CAP suggested a lower incidence of 1.6/1000.[6] A UK study of prospectively collected patients with lower respiratory tract infection in the community estimated the annual incidence of CAP in a much smaller defined population as 4.7/1000.[7]

The hospitalised population

Approximately 5% of acute medical admissions to UK hospitals are caused by CAP (HESonline.org.uk), resulting in over 100,000 hospital admissions in England and Wales annually.[8] The most recent study to examine the incidence of CAP estimated the annual incidence amongst adults (age ≥18 years) in Germany to be 2.75-2.96/1000.[9] The number of patients (adults and children) with CAP admitted to UK hospitals has risen from 1.48/1000 to 1.98/1000 population between 1997 and 2005, with the annual incidence highest in older adults (age ≥85: 22.2/1000; age 75-85: 8.8/1000; age 65-75: 3.6/1000).[8] There has been a 128% increase in admissions with CAP to critical care over a similar period.[10]

This trend is also seen elsewhere in the world. A Danish study of adults hospitalised with CAP showed an increase in hospital diagnoses from 2.88/1000 to 4.42/1000 population between 1994 and 2004.[11] A similar study in the USA in adults aged more than 65 years showed an increase in annual incidence between 1988 and 2002 of 17/1000 to 22/1000.[12]

Financial cost of CAP

Due to the high incidence of CAP in the general population, substantial costs are attributed to CAP in the UK. The last UK study on this subject was performed in 1997, which estimated that the total annual cost to the NHS was £440 million, with 96% of

this cost attributable to hospitalisation and 87% to bed-days used.[13] This cost assessment was performed on 1992-1993 prices, and so is likely to have increased substantially since. A more recent US study suggested that median hospital costs are US$8,654 per hospitalisation (interquartile range (IQR) US$5,457-US$16,027).[14] Estimates in the employed population are even higher, with a mean cost US$10,227 per episode, rising to US$15,822 in those patients who subsequently died.[15] As such, even small reductions in length of hospital stay (LOS) can have substantial cost benefits; a half-day shortening of LOS has been estimated to save US$724 per hospitalisation, translating to a potential saving of US$813 million nationally.[16]

Pneumococcal pneumonia

Introduction

Streptococcus pneumoniae (otherwise known as the "pneumococcus") is a Gram positive encapsulated organism responsible for the majority of bacterial respiratory infection worldwide. In the respiratory tract it causes CAP, otitis media (OM), and non-pneumonic lower respiratory tract infection (LRTI), but the pneumococcus also causes invasive disease such as bacterial meningitis (especially in the very young and old), septicaemia and endocarditis.

"Roughly lancet-shaped pairs of coccoid bacteria" were first described independently in human sputum by Louis Pasteur in France and George Sternberg in the USA in 1881. These organisms demonstrated pathogenic ability when injected into rabbits, causing a bacteraemia.[17] The capsular polysaccharide was first described by Neufeld in 1902, when observing microscopic capsular swelling (German: "quellung") and agglutination of pneumococci when exposed to specific pneumococcal anti-sera.

Even with rigorous diagnostic efforts, one or more causative pathogens may be identified in only up to 75% of individuals with CAP.[18-25] The pneumococcus is the commonest infectious agent responsible for hospitalised CAP and is found in up to 50% cases.[18-25] This remains the case in the more elderly population,[26] the more

severely ill patients,[21, 27] in primary care,[23, 28] and in a similar distribution worldwide.[19, 23]

Worldwide impact and distribution

Pneumococcal disease is estimated by the World Health Organisation (WHO) to cause 1.6 million deaths per year worldwide.[29] The most recent estimate of pneumococcal disease in children aged less than five years was a meta-analysis of estimates from different countries of the incidence of meningitis, CAP, and other pneumococcal disease in the year 2000.[30] This study estimated that 826,000 deaths in children annually were attributable to *S. pneumoniae*, with 91,300 in HIV positive children. 741,000 of these deaths were due to CAP.

This burden is borne particularly by the developing world. A study based in a rural population in Kenya of 16,570 children who had blood cultures drawn during an episode of CAP derived an incidence of community-acquired pneumococcal bacteraemia of 213 per 100,000 children aged <2 years, with 8.7% of in-hospital deaths attributable to pneumococcus.[31] These figures are likely an underestimate, because blood cultures have a low sensitivity for microbial aetiology (see chapter 3) and the majority of children in rural sub-Saharan Africa are not treated in hospital. The corresponding incidence in children aged <2 years in the USA has been estimated at 167 per 100,000 in 1998,[32] and in the UK in children aged <1 year between 1995 and 2000 was 38.6 per 100,000.[33] It has been postulated that the disparity between IPD rates in the USA and Europe is attributable to different rates of drawing blood cultures, and that there is therefore significant under-reporting of disease in Europe.[34]

Risk factors

Pneumococcal disease has specific demographic associations. A study of 609 subjects with pneumococcal bacteraemic CAP showed associations with those aged ≥65 years (odds ratio (OR) 31.3), lack of high school education (OR 2.7), and low income (OR 10.5 for annual income <$US6000).[35] Robinson and colleagues found

that in a US cohort of IPD, HIV/AIDS, asplenia and significant co-morbidity were risk factors (table 1.1), and over 50% of patients aged between 2 and 65 years dying from IPD had an identifiable underlying condition for which pneumococcal vaccination would be indicated.[32] Age-specific incidence of IPD was highest in those aged <2 years (166.9 per 100,000) and ≥65 years (59.7 per 100,000), with mortality highest in those aged ≥65 years (20.6%). Other published statistically significant ORs identified for developing IPD include asthma (2.4),[36] diabetes mellitus (1.9),[37] and cigarette smoking (4.1).[38]

Risk factor for IPD	Mortality rate (%)
None	4.0
HIV infection	7.1
AIDS	10.0
Diabetes mellitus	6.7
Alcohol abuse / cirrhosis	18.3
COPD	12.4
Asplenia	15.1
Congestive cardiac failure	27.4
Coronary artery disease	19.2
Malignancy, excluding haematological	21.6
Age ≥65 years	16.6
Any indication for pneumococcal vaccination	11.7

IPD: invasive pneumococcal disease; HIV: human immunodeficiency virus; AIDS: acquired immunodeficiency syndrome; COPD: chronic obstructive pulmonary disease. Adapted from Robinson et al., 2001.[32]

Table 1.1. Mortality for IPD in different at-risk groups.

Concluding remarks

The scale of the challenge posed to health services by CAP is huge. In addressing this, a strategy is required which incorporates both improved physician practice and enhanced awareness of CAP microbiology (particularly with regards to the most prevalent pathogen, *Streptococcus pneumoniae*, and its prevention with vaccination). Chapters 2 and 3 review what is already known about these two issues, and chapters 4 to 12 describe relevant clinical studies performed as part of this thesis.

Chapter 2: Pneumococcal disease and vaccination

“…the captain of the men of death”

Sir William Osler

Introduction

This chapter will describe the pathogenesis and transmission of pneumococcal pneumonia, and examine the current and future vaccine strategies aimed at its prevention.

Colonisation and transmission

The mechanisms by which *S. pneumoniae* causes disease and is transmitted are not fully understood. It is thought that *S. pneumoniae* initially colonises the upper respiratory tract, and thereafter may spread locally (to cause disease in the sinuses and middle ear) or be aspirated to the alveoli (causing CAP and thereafter IPD).

Nasopharyngeal carriage

Characteristics

The oral cavity and nasopharynx have a commensal flora comprising hundreds of different organisms.[39] *S. pneumoniae* and *Haemophilus influenzae* are thought to be the most pathogenic prevalent commensal organisms carried in the upper respiratory tract, and are acquired within the first few months of life.[40, 41] Carriage is asymptomatic, but disease is usually caused by the same serotype as was previously present as a coloniser,[41-43] suggesting that colonisation precedes development of invasive or local disease.

Prevalence

Point studies describing rates of carriage vary substantially between different ages and geographical locations, but are generally highest around two years of age, at around 50% (table 2.1). Higher colonisation rates have been observed in children attending day care centres (OR 1.6-3.4),[44] in members of families with young children,[45-49] and in children who have received prior antibiotics.[47] Point carriage rates in adults (aged >17 years) are substantially lower, estimated at between 2% and 13%.[45, 50-55] This implies that infants may act as a reservoir for pneumococcal disease, as carriage precedes disease, and the rate of carriage in adults is low.

Study	Point carriage rate (%)	Age (months)	Country
Healthy children			
Coles 2009 [56]	82.9	1-36	Nepal
Huang 2009 [57]	23-30	3-84	USA
Millar 2008 [58]	59-65	1-60	USA
Roche 2007 [59]	51	6-72	UK
Bogaert 2006 [60]	55	24	Netherlands
Hammitt 2006 [52]	59-61	1-48	Alaska
Hussain 2005 [49]	52	1-24	UK
Regev-Yochay 2004 [61]	43	1-40	Israel
Soewignjo 2001 [62]	48	1-24	Indonesia
Syrjanen 2001 [63]	43	24	Finland
Parry 2000 [64]	49.4	60	Vietnam
Lopez 1999 [47]	36	72	Spain
Mbelle 1999 [65]	26-30	1-2	South Africa
Hendley 1975 [45]	35	Pre-school	USA
RTI			
Coles 2009 [56]	76.7	1-36	Nepal
Syrjanen 2001 [63]	56	24	Finland

RTI: respiratory tract infection

Table 2.1. Point estimates from nasopharyngeal swab studies of childhood pneumococcal carriage rates in children.

In contrast to point prevalence studies, longitudinal studies have suggested that due to the dynamic nature of pneumococcal colonisation, over a longer period the majority of infants will be at least transiently colonised with pneumococcus. A population of children in Oxford had acquired pneumococcus at least once in 97% cases by the age of two years.[66] Children may be colonised sequentially with different serotypes, with one study of day care children reporting a mean of 3.6 different strains acquired over the course of a year.[67] This same study reported that over a course of a year, 46/47 children attending a single day care centre acquired pneumococcal carriage on at least one occasion. In a Gambian population, 97% of children and 87% of adult close contacts were colonised at least once over the course of a year.[68]

Competition

Due to the large number of different colonising species in the naso-orophaynx,[39] colonisation is a dynamic process, with competition for the niche occurring between species. Carriage of α-Haemolytic Streptococci is associated with lower rates of pneumococcal OM in children (65% vs. 14%),[69] and these isolates have an inhibitory effect on pneumococcal growth *in vitro*.[70] Competition also occurs between pathogenic species. Pneumococcal carriage in healthy children is inversely correlated with carriage of *Staphylococcus aureus*, suggesting a mutually inhibitory effect.[61, 71] Lysenko and colleagues showed in a mouse model that co-colonisation with *Haemophilus influenzae* and *S. pneumoniae* resulted in rapid neutrophil-mediated killing of the latter, whereas colonisation persisted when either organism was given separately.[72]

Transmission

Transmission is thought to occur by direct contact with the respiratory secretions of an individual carrying pneumococcus. The highest rates and longest duration of colonisation are found in infants, and therefore studies have investigated how infants both become colonised with and transmit pneumococci.

Transmission between children in day care

Pneumococcal transmission from child to child occurs readily in a close contact situation such as a day care centre. A longitudinal study of 262 toddler day care attendees and their 36 younger siblings showed that of 71 newly acquired pneumococcal strains in the younger siblings, 54 (76%) were isolated at least once in the older sibling's day care centre in the preceding six months.[73] A longitudinal study in a single day care centre with eleven sampling periods over the course of a year described the transmission dynamics of nasopharyngeal carriage of *S. pneumoniae*.[67] Several pneumococcal clones were identified that colonised a single child, with the same clone proceeding to colonise several other children over the course of the study. A further study in a Finnish cohort estimated that on average 2.7 new outbreaks of pneumococcal colonisation are generated per day care centre per month, involving an average of 7.6 children for an average of 2.8 months.[74]

Transmission from children to adults

Transmission has been studied between infants and other same-household contacts regardless of age. Having a child less than six years old in day care has been significantly associated with development of IPD in adult household contacts (OR 2.3).[38] In a Finnish longitudinal study, children aged more than six months were more likely to be colonised with *S. pneumoniae* if a family member was also colonised (OR 3.6).[48] A study of 39 households in a slum community in Brazil showed that nine households had more than one family member colonised with the same pneumococcal strain, implying transmission between the two members.[75] A longitudinal study of fortnightly nasopharyngeal swabs in nineteen households in Gambia over a twelve month period showed that the odds of being colonised with *S. pneumoniae* were significantly greater if other carriers were present in the household, for both adults and children.[68] However, neither of these two studies showed a correlation between large family size and chance of pneumococcal carriage. A ten month longitudinal study of 121 families in the UK showed that 64% of new colonising

pneumococcal serotypes within the household were introduced by children aged less than three years, compared with 1% for those aged 5-17 years.[49] Individual pneumococcal carriage was associated with increased age-stratified risk ratios for carriage in other family members of 1.42, 1.25, and 2.25 for those aged 0–2, 3–4 and ≥5 years respectively. Finally, day care centre employees have a relatively high pneumococcal colonisation rate for adults, at around 21.7%,[76] suggesting that they are continually being exposed to and colonised by pneumococci from children with whom they work.

Intra-familial transmission has also been directly linked with disease as well as asymptomatic colonisation. A study of eleven families where there were episodes of concurrent or closely related acute OM amongst siblings showed that of thirteen disease clusters, twelve were of identical nasopharyngeal strains of pneumococcus.[43] However, there have been no similar studies to date for pneumococcal CAP.

Transmission between adults

Pneumococcal outbreaks amongst adults are rare, implying that pneumococcal transmission between adults is limited. The case reports that exist are often in an institutional setting. Outbreaks of pneumococcal disease of the same serotype and/or clone have been described in hospitals,[77-83] nursing homes,[84] military barracks,[85, 86] homeless shelters,[87, 88] nurseries,[89] and prisons.[90] In the most comprehensive study to date, 17 out of 74 (23%) residents of a nursing home were found to be colonised with the same pneumococcal serotype (a drug-resistant 23F) as 7 out of 11 residents of the same care home admitted to hospital with CAP.[84] The same strain was also found in 2 of 69 of the nursing home staff who had close contact with the affected residents.

Summary

Pneumococcal transmission occurs between infants at day care centres and between infants and other family members (both children and adults) within a household. Widespread colonisation is also associated with outbreaks of disease in concentrated

adult populations, particularly in an institutional setting and those at risk of pneumococcal disease such as the elderly and inpatients.

The pneumococcal capsule and serotypes

Structure and role

The polysaccharide capsule surrounds the pneumococcus and is covalently bound to the cell wall. 91 distinct capsular types have been discovered to date, with each serotype defined by the ability to cross-react to mutual immune anti-sera.[91, 92] The capsule consists of a polysaccharide coat with embedded proteins, and provides protection from host defences in a number of ways:

- The polysaccharides are negatively charged,[93] potentially helping to repel negatively charged nasopharyngeal mucus;[94]
- It inhibits opsonisation with complement and phagocytosis;[95]
- It reduces bacterial capture in neutrophil extracellular traps.[96]

The pneumococcal capsule is a key virulence factor for the development of pneumococcal disease. This was first demonstrated in 1931 by Avery and colleagues, who showed that decomposition of the capsule of a serotype 3 pneumococcal clone protected mice against subsequent challenge with the organism.[97] Later experimental studies in mouse models have shown that invasive disease is impossible for pneumococcal mutants where the capsular polysaccharide is no longer bound to the cell wall.[98] Furthermore, the virulence of a serotype 5 isolate was almost abolished in a mouse model by genetic switching of the capsular expression to serotype 3.[99] In humans, strains lacking a capsule have only been reported to cause superficial disease.[100]

Distribution in disease

The distribution of serotypes causing pneumococcal disease has been well described in IPD. The results from a meta-analysis by Hausdorff and colleagues of over seventy

IPD data sets worldwide in adults and children before the introduction of the 7-valent childhood pneumococcal vaccine (PCV-7 – see later in this chapter) are presented in table 2.2.[101] The most recent study in a pneumococcal UK population of all ages was published in 2008, comprising 1388 blood and sputum cultures collected between 2001 and 2006 (table 2.3).[102] The serotype distribution from other major studies published since 2000 (and therefore not included in the meta-analysis by Hausdorff and colleagues) are also shown in table 2.3. These data suggest substantial variation in serotype distribution both geographically and between age groups. This has implications for the development of pneumococcal vaccines, a subject discussed in more detail later in this chapter.

Area of origin	Order of invasive serotype by prevalence						
Adults	**1st**	**2nd**	**3rd**	**4th**	**5th**	**6th**	**7th**
USA	4	14	9V	6A/B	12F	19A/F	23F
Europe	14	3	9V	19A/F	1	6A/B	23F
Oceania	14	4	19A/F	9V	1	6A/C	3
Asia	1	3	6A/B	6	19A/F	7	14
Africa	1	19A/F	14	6	3	12	7A/F
South America	1	6A/B	3	18C	12F	23F	19A/F
Children							
USA	14	6A/B	19A/F	18C	23F	9V	4
Europe	14	6A/B	19A/F	18C	23F	9V	1
Oceania	14	6A/B	19A/F	23F	18C	7A/F	4
Asia	1	19A/F	6A/B	5	14	7A/F	23F
Africa	6A/B	14	1	19A/F	23F	5	15
South America	14	6A/B	5	1	19A/F	23F	18C

Adapted from Hausdorff and co-workers, 2000.[101]

Table 2.2. Differences in geographical pneumococcal serotype distribution.

Study	Study year	n	Location	14	8	9V	23F	3	6A	6B	4	1	19F	7F	19A
Adults and children															
Trotter 2010 [103]	1998-1999	2011	UK	17.1	7.3	8.5	6.5	5.5	3.5	5.5	5.7	7.3	4.9	3.8	3.4
Liao 2010 [104]	2000-2005	221	Taiwan	29.0	0	2.7	14.0	11.3	0	13.1	1.8	0.5	11.3	0.5	0.5
Farrell 2008 [102]	2006	354	UK	15.3	5.7	9.0	6.2	5.4	3.4	4.0	6.2	17.2	2.8	5.1	3.1
Harboe 2009 [105]	1977-2007	18858	Denmark	9.4	4.6	5.5	3.8	5.7	3.1	3.9	8.9	14.6	3.2	7.6	1.9
Jansen 2009 [106]	2004-2006	1107	Netherlands	12.6	7.8	8.8	6.1	6.1	2.8	2.4	9.0	6.0	3.3	12.6	3.0
Foster 2008 [107]	1996-2005	2691	UK	18.4	6.2	7.7	6.7	5.4	-	5.9	5.2	7.5	3.8	-	3.8
Sjöström 2006 [108]	1993-2000	494	International	14.6	2.8	9.9	8.1	7.7	2.4	4.3	6.3	5.9	4.3	6.9	3.8
Robinson 2001 [32]	1998	3610	USA	17.6	-	8.5	7.4	3.3	4.3	7.7	10.5	2.4	5.5	2.8	3.3
Adults															
Chiba 2010 [109]	2006	303	Japan	7.6	n/a	4.6	5.3	7.9	5.0	10.2	7.3	2.3	5.3	n/a	3.3
Lujan 2010 [110]	1999-2009	294	Spain	7.6	n/a	n/a	n/a	12.3	n/a	n/a	n/a	18.9	n/a	n/a	n/a
Henriques 2000 [111]	1993-1995	354	International	30.8	4.2	12.1	8.2	13.6	0.8	2.8	5.1	8.5	6.5	8.5	5.9
Children															
Chiba 2010 [109]	2006	193	Japan	13.0	n/a	6.2	11.9	2.1	6.7	22.3	6.2	2.1	14.0	1.0	6.2

Figures for individual serotypes represent % of each serotype within the pneumococcal cohort.

Table 2.3. Serotype distribution within pneumococcal bacteraemic cohorts prior to introduction of 7-valent conjugate vaccine.

No studies have been performed in cohorts of non-invasive disease; that is to say, patients who have evidence of infection with *S. pneumoniae*, but do not have positive blood or sputum cultures. The sensitivity of culture-based investigations is low (see chapter 3), and so for a substantial proportion of those patients with pneumococcal CAP a serotype is not reported. Thus the serotype distribution for *all* patients with pneumococcal CAP is currently unknown.

Variation in disease spectrum by serotype

Invasive potential

The relationship between carriage and invasive disease is complex and not fully understood; colonisation in children is common, but invasive disease rare. Estimation of a serotype's "invasiveness" by examining studies of IPD may be misleading; a high representation of a particular serotype in invasive cohorts may represent high exposure of children to the serotype, rather than that serotype having a particularly high invasive potential. Brueggemann and colleagues correlated a series of IPD serotypes in children with serotypes prevalent in a carriage study within a population of young children during the same time period.[112] This enabled calculation of ORs for "invasiveness", or the potential different individual serotypes have for causing invasive disease if carried in the nasopharynx when compared with all other serotypes. Serotypes 4 (OR 12.1), 1 (OR 9.6), 18C (OR 5.8), and 14 (OR 8.8) were the most invasive in this study, with 23F being least invasive (OR 0.4). A similar study in Finland compared all IPD isolates in children aged <2 years with an age-matched point prevalence study from a single town in Finland.[113] Serotypes 14 (OR 4.1), 18C (OR 3.3), 19A (OR 2.9) and 6B (OR 1.6) were the most invasive, with 6A (OR 0.5), 35F (OR 0.2) and 11A (OR 0.05) the least. Serotype 1 was not represented in this data set, and serotype 7F was of borderline significance. These findings were replicated using similar methodology, finding that serotypes 1, 4, 7F and 9V were particularly invasive.[114] A meta-analysis performed by Brueggemann using seven similar international cohorts reported that, using serotype 14 as a comparator, serotypes 1, 5 and 7F were the most invasive, 4 equivalent in invasiveness, and all

others less invasive, with the least invasive being serotypes 3, 15 and 6A.[115] In addition, these studies have found that the higher the invasive potential, the lower the prevalence of the serotype within carriage studies, suggesting that those serotypes carried for a long time have a lower invasive potential.

The only study to estimate serotype invasiveness in *adults* was conducted by Trotter and co-workers, which compared serotype carriage rates in adults from a previous study with rates of the same serotypes in contemporaneous national IPD surveillance.[103] This study found high case:carrier ratios (>100 cases per 100,000 carriers) for serotypes 4, 8, and serogroup 9. Data for serotypes 1 and 5 were not reported, and 7F was not represented within the carriage cohort.

A second way of measuring the invasiveness of a given serotype is to estimate the attack rate, or the proportion of each new acquisition of pneumococcal carriage that goes on to develop IPD. Sleeman and colleagues showed that certain serotypes were associated with attack rates of at least 20 per 100,000 acquisitions (higher invasive potential; 1, 5, 9A, 14, 18C, 19A, 9V, 4, 7F, 8, 12F), whereas others were associated with an attack rate of <10 per 100,000 acquisitions (lower invasive potential; 19F, 6B, 23F, 6A, 3).[66] A final method for estimating invasiveness is to compare the distribution of carriage serotypes between patients with CAP and healthy controls, the assumption being that during disease the colonising and infecting serotype will be the same. Using this method in children, Greenberg and co-workers found that serotypes 1, 5, 22F, 7F, 14, 9V, and 19A were more prevalent in disease than health.[116]

In summary, allowing for heterogeneity between studies, serotypes 1, 5 and 7F seem have the highest propensity to cause invasive disease following colonisation, in contrast to 3, 6A, and 19F (among others). However, the majority of these data are gathered from studies of children, and all compare carriage and IPD data from different populations due to the generally low incidence of IPD.

Demographics, disease course and outcome

Brueggemann and colleagues found that invasiveness was correlated with serotype rather than clonal type or genotype,[112] implying that capsular type rather than genotype may produce differences in clinical disease. Therefore investigators have examined a variety of other clinical aspects of pneumococcal disease by serotype. All of the studies to date have been in cohorts of IPD, and therefore have not included the majority of pneumococcal CAP, which is not associated with bacteraemia.

Mortality

Differences in mortality by serotype are perhaps the best studied of the clinical phenotypes in adults. In an early cohort of 325 patients with pneumococcal bacteraemia, the highest mortality was associated with serotype 3, but no attempt was made to correct for age.[117] This finding has been replicated elsewhere.[108, 111, 118] A retrospective study of 464 IPD isolates did correct for age and other confounders, and still found that serotype 3 was associated with higher mortality (relative risk (RR) of death 2.54) and serotype 1 lower mortality (RR 0.23) in a multivariate analysis.[119] A large study from the Active Bacterial Core Surveillance Network in the USA, using serotype 14 as a reference, showed significantly increased adjusted OR's for mortality for serotypes 3, 11A, 19F and 23F.[120] In a similar study in the Netherlands (n=1142), where (in contrast to the other studies mentioned) rates of all pneumococcal vaccination in adults are very low, case fatality rates for a group of serotypes with low invasiveness (3, 6B, 9N, 16F, 18C, 19F, and 23A) were higher than the reference group (high invasiveness; comprising serotypes 1, 5, 7F, 15B, 20, and 33F) in a multivariate analysis (adjusted OR 2.6).[106] A recent study found that patients with IPD from group of low invasiveness serotypes (3, 6A, 6B, 8, 19F and 23F) had an OR for 30-day mortality in a logistic regression analysis of 10.3 compared with IPD from the more invasive serotypes 1, 5 and 7F.[110] IPD from highly invasive serotypes was associated with younger age, better pre-morbid status and an increased rate of para-pneumonic effusion or empyema. However, it should be noted that the assumptions on "invasiveness" in this study for groups of serotypes were derived from studies on

childhood disease as described earlier, and are not necessarily applicable to adult disease. A meta-analysis of IPD studies has also shown that serotypes 3, 6A, 6B, 9N, and 19F are associated with increased 30-day mortality, and 1, 7F and 8 with lower 30-day mortality, using the 30-day mortality for serotype 14 as a comparator.[121] In addition, 30-day mortality was positively correlated with carriage prevalence, but inversely correlated with invasive potential; in other words, a) less invasive serotypes were associated with higher mortality, and b) highly invasive serotypes were associated with a low duration of nasopharyngeal carriage. However, a study by Alanee and co-workers found no association between serotype or serotype group and 30-day mortality in 796 prospectively recruited adults.[122] In summary, the majority of studies (albeit in IPD rather than invasive and non-invasive CAP) agree that serotype 3 is associated with a higher adjusted mortality, and serotypes 1 and 7F with a lower mortality.

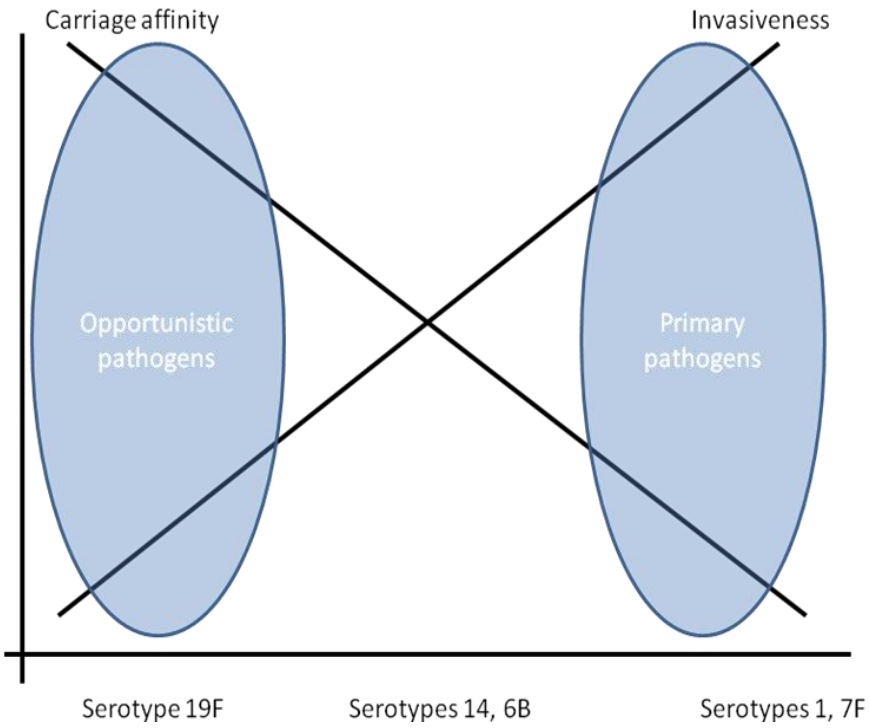
Age

The serotypes found in invasive disease in children vary substantially from those seen in adults (table 2.3). A retrospective study of over 7,000 patients with invasive pneumococcal isolates showed that the relative risk of disease due to serogroup 1 fell with increasing age, whereas it increased with age for serogroups 3 and 8,[123] a finding replicated elsewhere.[124] A study of 494 patients with IPD (of which 83% had CAP) found that serotype 1 was not represented at all in those aged over 65, in contrast to 23F which was rarely seen outside of this age group.[108] However, for all other serotypes in this study the interquartile ranges for age were wide. A recent study looked at over 7000 cases of IPD, and found that serotypes 14, 6B, 19F, and 18C were more common in children (age ≤16 years), with serotypes 3 and 4 more common in adults.[125] When compared with other age groups, the only serotype within the age group 16-64 years (including those patients of child-bearing age) that had significantly lower prevalence was serotype 14. In another study, “paediatric serotypes” (6B, 9V, 14, 19F, and 23F) represented 32.5% of IPD in adults aged 35-49, compared with 51.2% in adults aged >85 years.[126] This re-emergence of

paediatric or infant serotypes in the very elderly (particularly with an increase in disease due to serogroups 14 and 23) has been reported elsewhere, and perhaps reflects either deterioration in the immune system with age, or increased contact with young grandchildren in the older age groups.[124] It also may support targeted vaccination of older people with pneumococcal conjugate vaccines.

Clinical presentation

A meta-analysis by Hausdorff and colleagues found that serogroups 1 and 14 were more often represented in data gathered from blood cultures, serogroups 6, 10 and 23 in cerebrospinal fluid, and 3, 19 and 23 in middle ear fluid in children.[127] A study of 368 isolates in children found that serotype 1 was the cause in 24.4% of cases of CAP complicated by pleural effusion or empyema compared with only 3.6% of patients without these complications,[128] a finding replicated elsewhere.[129] A study containing 598 IPD isolates suggested that serotype 3 was more associated with septic shock (present in 39% of patients with shock vs. 24% in those without shock, OR 2.24), and conversely, serotype 1 with not developing shock (present in 2% of patients with shock vs. 10% in those without shock, OR 0.26).[130] Serotype 3 has also been associated with the development of necrotizing CAP in children (79% vs. 20% for other serotypes; OR 14.7).[131] In a study by Sjöström and colleagues, lower disease severity at presentation, as measured by proportion of patients with APACHE II scores less than 11, was seen with serotype 1 (21%), 4 (35%) or 7F (26%), compared with 3 (63%), 6B (76%) or 19F (71%).[108] In addition, patients with infection due to invasive serotypes (1 and 7F) had a low rate of co-morbidity (43%) compared with less invasive serotypes (3, 6A, 6B, 8, 19F, and 23F: 75%). Experiments using a mouse model from the same group showed that intra-peritoneal challenge with serotypes 1 and 7F produced a much lower inflammatory response (as measured by TNF-α levels) than serotypes 4, 6B, or 19F.[132] The authors therefore concluded that highly invasive serotypes such as 1 and 7F act as *primary* pathogens, but serotypes with low invasive potential such as 19F are acting as *opportunistic* pathogens, a concept illustrated in figure 2.1.



Adapted from Sjöström and colleagues.[108]

Figure 2.1 Illustration of the hypothesis of invasiveness versus carriage affinity.

Variation in *in vitro* characteristics

The molecular mechanisms underlying the differences in serotype behaviour seen in clinical disease are not fully understood, and this section aims to highlight that differences are seen by serotype *in vitro* as well as *in vivo*. Serotype 3, which seems to be associated with a high mortality but low invasive potential in the majority of studies described above, is known to have a particularly thick polysaccharide coat,[121, 133] which helps to resist phagocytosis,[134, 135] and this is associated with increased virulence in mice.[136] Certain serotypes have been found to be more susceptible to complement binding (serotypes 3 and 4 more so than 6A and 14).[137] Splenic clearance of pneumococci is mediated at least in part by SIGN-R1, a C-type lectin expressed by splenic macrophages.[138, 139] Each of these receptors has affinities for particular polysaccharide ligands,[140] implying variety in the recognition of different pneumococcal serotypes. Furthermore, different serotypes have been associated with varying LytA-mediated lytic responses of pneumococcal isolates to penicillin and vancomycin.[141] In this *in vitro* study un-encapsulated strains of pneumococcus were far more susceptible to lysis than encapsulated strains, and serotypes 3 and 14 were more susceptible than 1, 4, 6B and 23F. However, more work in this area is required to more precisely define the role of different capsular types in causing pneumococcal disease.

Nasopharyngeal carriage

There are significant differences between the serotype distribution in IPD cohorts and carriage cohorts. Point estimates for the distribution of serotypes in pneumococcal carriage studies are shown in table 2.4, and comparison can be made with the distribution of invasive disease as seen in table 2.3. Of note, serotypes 19F, 6A/B and 23F are frequently found in carriage point studies in both adults and children, but serotypes 1 and 5 are rarely found, even in those populations such as Africa where these serotypes are more strongly found in IPD cohorts (table 2.3).

Study	Country	n	Order of serotype prevalence				
Children			**1**	**2**	**3**	**4**	**5**
Bogaert 2001 [44]	Netherlands	259	19F	6B	6A	23F	9V
Syrjanen 2001 [63]	Finland	329	6B	6A	11	19F	23F
Sa-Leao 2008 [67]	Portugal	414	19F	23F	6A	14	10A
Parry 2000 [64]	Vietnam	911	19	23	14	6	18
Soewignjo 2001 [62]	Indonesia	484	6	23	15	33	19
Rusen 1997 [142]	Kenya	207	13	15	14	6B	19F
Mbelle 1999 [65]	South Africa	239	19F	6B	23F	6A	19A

Table 2.4 Point estimates for the distribution of pneumococcal serotypes in carriage studies in children before the introduction of the pneumococcal vaccine.

Larger studies are often confined to children given the much higher carriage prevalence/incidence in this age group, and studies in adults are usually limited to those with close contact with children rather than age-stratified population-based studies. One study in a cohort of children and adults in an Australian indigenous population post-licensure of the 7-valent pneumococcal vaccine for children (PCV-7 – see later in this chapter) showed the five commonest carried serotypes in adults were 6B, 7C, 16F, 19F and 34.[143] This study also showed an outbreak of serotype 1 carriage, which is very rarely seen in any carriage studies in adults or children. A study of Alaskan villagers of all ages before PCV-7 was introduced found that the five commonest serotypes carried by adults were 11A, 19F, 35B, 6B and 16F.[52]

Carriage dynamics also vary substantially between serotypes. In a longitudinal pre-pneumococcal vaccine study in a day care centre some serotypes were carried for a short duration but with a high propensity for transmission (10A and 19A) whereas others were carried for longer periods (19F and 23F).[67] A large longitudinal study from Gambia showed that serotype 9V was carried for an average of two weeks and serotype 14 for 37 weeks.[68] In the same study the average duration of pneumococcal carriage was 28 weeks for children aged less than one year, but only three weeks for adults forty years or more. In a further study pneumococci were carried for an average of 51 days for children aged five years and nineteen days for older family members.[144]

Summary

Different pneumococcal serotypes have profoundly different clinical, microbiological, and epidemiological characteristics, to the extent where each serotype may be thought of as a distinct clinical entity. However, data in these studies are mainly derived from IPD or carriage cohorts, and little is therefore known of non-invasive disease.

Pneumococcal polysaccharide vaccine

Origin of the vaccine

Pneumococcal vaccines work by inducing protective antibody responses to the capsular polysaccharide antigens, and often are defined by the number of different serotypes covered (their "valency"). The first pneumococcal vaccines for adults were trialled in 1977 in a cohort of South African gold miners (6- and 13-valent vaccine),[145] and in Papua New Guinea (14-valent vaccine),[146] and these trials showed a reduction in IPD within the vaccinated populations of 79% and 84% respectively. These vaccines were subsequently replaced by a 23-valent pneumococcal polysaccharide vaccine (PPV; Pneumovax®) which has been used in the UK since 1983. PPV contains capsular polysaccharide components of 23 of the commonest bacterial pneumococcal serotypes (table 2.5), in particular those serotypes implicated in invasive disease or antibiotic resistance.

Target groups

In many countries vaccination with PPV is offered to younger adults who are at risk of pneumococcal disease (table 1.1) and to older adults (65 years of age or more) without specific risk factors.[147] It is not appropriate for use in children aged less than two years due to their relatively immature immune system, but can be given to children aged more than two years who have already received the 7-valent childhood pneumococcal conjugate vaccine (PCV-7; see next section).

Duration of protection and re-vaccination

Antibody levels persist for at least five years in the healthy adult, but start to decline from thirty days post-vaccination.[148-150] However, a proportion of older patients have poor IgG responses to PPV,[151] and the elderly may also have reduced opsonophagocytic activity from the induced anti-pneumococcal IgG.[152] The duration of clinical protection is debated. Shapiro and colleagues performed a case control study suggesting that protection decreases slowly over time in all age groups, particularly so in the elderly (85% protective efficacy in those aged <55 years; 32% in those aged 74-

85 years).[153] However, using an indirect cohort analysis Butler and colleagues showed good persistence of vaccine protection up to nine years.[154]

As PPV induces a T cell-independent response, it is not possible to produce a "booster" effect by administering a repeat vaccination. Re-vaccination at five years results in repeated antibody rises, but at a slightly lower level than following the first vaccination,[148, 149, 155] with a higher rate of local side effects.[149, 155, 156] Consequently re-vaccination should never be offered within three years of first vaccination, and should only be considered in patients at high risk of pneumococcal disease.

Vaccine efficacy

Polysaccharides, as contained in PPV, are poorly immunogenic when compared with proteins, and only induce a T cell-independent response.[157] A recently updated Cochrane review showed a reduction in IPD following PPV (OR 0.26; efficacy 74%),[158] but showed no effect on reducing mortality and was inconclusive concerning a reduction in all-cause CAP. A number of other studies, including a further meta-analysis looking primarily at studies of higher quality, have shown no demonstrable reduction in all-cause or pneumococcal CAP attributable to PPV use in the elderly.[159-162] Indeed, in one large cohort study a trend was seen towards an *increase* in the incidence of CAP following vaccination.[163] However, using pneumococcal CAP as an outcome is complicated by the lack of a definitive microbiological test for *S. pneumoniae*; therefore most studies either look at radiological CAP of any cause, or radiological CAP associated with IPD, which comprises only a small fraction of patients with CAP. PPV is not associated with a protective effect in patients who have previously had CAP,[164] but may reduce severity of hospitalised disease as measured by intensive care admission,[165] length of stay,[166] and time to symptom resolution.[167] Despite these positive findings, at best PPV seems to provide modest protection against pneumococcal disease, and therefore efforts have been made to find alternative, more efficacious vaccines.

Conjugate vaccines

Origin

Due to the problems inherent in PPV as described above (in particular the inability to use it in children aged less than two years and the lack of efficacy in preventing CAP), further vaccine developments were required. The immunogenicity of the polysaccharides contained with PPV can be enhanced by conjugating to a highly immunogenic protein,[168] creating a pneumococcal conjugate vaccine (PCV). Conjugation of a protein to the vaccine also promotes a T cell *dependant* response, inducing a memory T cell response, and hence the ability to use multiple doses to achieve a booster effect.[169]

The first PCV to be introduced to vaccination schedules was PCV-7, for use in infants less than two years of age, in three doses at two, four, and thirteen months. Only seven serotypes are included in the vaccine, in contrast to the 23 in PPV, although these seven are thought to include the majority of prevalent and invasive serotypes encountered in the USA (table 2.3). However, this is not the case in the rest of the world, particularly Africa and Asia, where these seven serotypes represent only 60% and 45% of IPD serotypes respectively.[101]

Efficacy

Between 92% and 100% infants generate antibody after three PCV-7 doses.[169] It has proven efficacy in reducing:

- All-cause and pneumococcal OM in children;[170, 171]
- Hospital or outpatient visits due to OM;[172, 173]
- IPD in all children;[174-176]
- IPD in vaccinated children;[177-179]
- CAP in vaccinated infants;[179, 180]
- All-cause and pneumococcal CAP hospital admissions in children;[173, 181-183]
- PCV-7 serotype (VT) carriage in vaccinated infants;[184-187]
- Pneumococcal VT carriage in household contacts of vaccinated infants;[58, 184]

- Pneumococcal VT carriage in unvaccinated infants;[188]
- Pneumococcal VT carriage in adults;[52]
- VT and all cause IPD in adults;[120, 176, 189]

A recent meta-analysis incorporating these studies calculated a reduction in vaccinated children of 89% for VT IPD, 55-57% in VT OM, and 29-32% in radiographically confirmed CAP.[190] Of particular note, PCV-7 reduces VT colonisation in unvaccinated contacts, and IPD in unvaccinated adults. This suggests that large scale vaccination of children may be promoting a "herd immunity" effect. In addition, all pneumococcal disease is thought to be preceded by nasopharyngeal carriage, and the highest rates of pneumococcal carriage are in children. Therefore, the reduction in pneumococcal carriage in children may be reducing transmission to adults, and thereby reducing adult pneumococcal disease. However, this theory is as yet unproven.

Serotype shift

PCV-7 contains only seven of the 91 pneumococcal serotypes.[92] Thus while significant reductions are expected in VT serotypes across the pneumococcal disease spectrum, uncertainty surrounds the impact of vaccination on non-PCV-7 vaccine-type (NVT) serotypes. As discussed in the previous section, all-cause IPD rates have fallen following introduction of PCV-7. However, an increase in NVT and vaccine-related serotypes (defined as the same serogroup as a VT serotype, but different serotype; for example, 19A and 19F) at the expense of VT serotypes has also been seen. Several carriage studies have shown an increase in NVT serotypes concomitant with a decrease in VT serotypes.[57, 58, 187, 191] IPD studies have shown an increase in the total number and proportion of cultured NVT serotypes, an effect seen in both PCV-7 vaccinated and unvaccinated children, and adults (table 2.6). Of note, serotype 19A has significantly increased in incidence in the majority of IPD studies. Increases in the NVT serotype 19A in otitis media in children in one study interestingly started to occur *before* the introduction of PCV-7.[192] Antibiotic resistance within this group also

increased from 10% to 50% over the study period, implying that this increase may have been driven by antibiotic over-use.

Vaccine	Serotypes covered
PPV	1, 2, 3, **4**, 5, **6B**, 7F, 8, 9N, **9V**, 10A, 11A, 12F, **14**, 15B, 17F, **18C**, 19A, **19F**, 20, 22F, **23F**, 33F
PCV-7	**4, 6B, 9V, 14, 18C, 19F, 23F**
PCV-9	1, **4**, 5, **6B**, **9V**, **14**, **18C**, **19F**, **23F**
PCV-10	1, **4**, 5, **6B**, 7F, **9V**, **14**, **18C**, **19F**, **23F**
PCV-11	1, 3, **4**, 5, **6B**, 7F, **9V**, **14**, **18C**, **19F**, **23F**
PCV-13	1, 3 ,**4** , 5, 6A, **6B**, 7F, **9V**, **14**, **18C**, 19A, **19F**, **23F**

Shared serotypes are in bold. PPV: pneumococcal polysaccharide vaccine; PCV: pneumococcal conjugate vaccine.

Table 2.5. Pneumococcal vaccine serotype coverage.

Study	Setting	N	Time period	Emergent serotypes	Reduction in VT disease	Increase in NVT disease
Lexau 2005 [120]	US, ≥50 years	8821	1998-2003	n/a	55%	5%
Singleton 2007 [193]	Alaska; infants	1478	1995-2006	19A	96%	140%
Hicks 2007 [194]	US; young children	4073	1998-2004	3, 6A, 12F, 15, 19A, 22F, 33F	97%	22%
Hicks 2007 [194]	US; adults	6324	1998-2004	12F, 15, 16F, 19A, 23A, 33F, 35	76%	10%
Jacobs 2008 [195]	US; all ages	1235	1999-2007	6C, 19A, 22F, 33F	92%	19%
Tyrrell 2009 [196]	US; all ages	2768	2000-2006	3, 5, 8, 11A, 12F, 19A, 22F	61%	236%
Tsigrelis 2009 [197]	US; ≥50 years	50	1995-2007	3, 19A	64%	72%
Salleras 2009 [198]	Spain, infants	349	1997-2007	19A, 24F	55%	132%
Hsu 2010 [199]	US; age <18 years	433	2001-2007	19A	n/a	77%
Park 2010 [200]	US; vaccinated children	753	2001-2004	3, 6A, 7F, 12F, 15B/C, 19A, 22F, 33F, 38	n/a	n/a
Rodenburg 2010 [201]	Netherlands; <2 years	110	2004-2008	1, 7F	67%	44%
Rodenburg 2010 [201]	Netherlands; >2 years	2419	2004-2008	1, 22F	-1%	8%
Liao 2010 [104]	Taiwan, all ages	337	2000-2008	19A	-6.2%	-16.3%
Pilishvili 2010 [202]	US; <5 years	2422	1998-2007	3, 7F, 19A, 22F, 33F	100%	38%
Pilishvili 2010 [202]	US; aged 5-64 years	5444	1998-2007	3, 7F, 19A, 22F	89%	47%
Pilishvili 2010 [202]	US; ≥65 years	3414	1998-2007	3, 6A/C. 7F, 19A, 22F, 23A	92%	33%
Kaplan 2010 [203]	US; <16 years	1029	2001-2008	1, 3, 7F, 19A	n/a	n/a
Foster 2011 [204]	UK; infants	408	1995-2009	7F	83%	57%
Foster 2011 [204]	UK, aged >2 years	3382	1995-2009	7F, 19A, 22F	50%	18%

VT: serotype included in PCV-7; NVT: serotype not included in PCV-7 (including vaccine-related serotypes); “infants”: children aged less than 2 years; “children”: those aged less than 5 years.

Table 2.6. Studies showing a serotype shift in invasive pneumococcal disease since introduction of PCV-7.

Serotype shift has been implicated in a change in the spectrum of clinical disease, primarily in children. An increase has been documented in the incidence of a serious complication of CAP, para-pneumonic empyema, in the USA in children from 2.2 per 100,000 to 3.7 per 100,000 following the introduction of PCV-7,[205, 206] and this has primarily been caused by NVT serotypes 1, 3 and 19A.[207] However, the incidence of empyema also increased in the decade *prior* to introduction of PCV-7 in Israel (from 0.5 to 4.2 per 100,000 children), mainly due to serotype 1,[208] suggesting that epidemiological factors may also be implicated in this change. An increase in culture-positive pneumococcal necrotizing pneumonia from 13% pre-PCV-7 to 33% post-PCV-7 has been observed in children in Utah, USA, accompanied by an increase from 47% to 88% of NVT serotypes.[131] Serotype 3 was particularly associated with this increase. Reductions in IPD mortality have been seen since the introduction of PCV-7 in the USA of between 30 and 45 per 100,000 in adults aged more than 55 years.[209]

Therefore PCV-7 appears to be causing a shift in prevalent serotypes in IPD, which may be causing changes in the clinical disease spectrum, both by an increase in CAP complications such as empyema, and a reduction in mortality. However, the evidence for this effect to date is scanty, and may not be representive of non-invasive CAP, which forms the majority of disease. A rigorous observational study is required, linking the change in pneumococcal serotypes following the introduction of PCV-7 with a change in the clinical spectrum and outcome of invasive and non-invasive pneumococcal CAP.

Developments in conjugate vaccines

PCV-9 and -11

A response to the development of serotype shift has been to broaden the spectrum of serotypes covered by PCV. This is of particular interest in the developing world where the serotypes contained within PCV-7 do not reflect the serotype distribution of IPD, particularly with respect to serotypes 1 and 5 (table 2.2). A 9-valent vaccine

incorporating these two additional serotypes has been trialled in 19,922 children in South Africa, and found to reduce IPD due to serotypes in PCV-9 by 83% (65% in HIV infected children) and radiologically-confirmed CAP by 20-25%.[210] A randomised controlled trial of PCV-9 in over 17,000 Gambian children showed a vaccine efficacy of 37% for radiological CAP and 77% for IPD due to serotypes in PCV-9.[211] An 11-valent vaccine (PCV-11; adding serotypes 3 and 7F), has been trialled in over 12,000 children in the Philippines.[212] This showed a vaccine efficacy in all-cause radiographically confirmed CAP of 22.9%.

PCV-13

The most recent vaccine to be licensed for use in the developed world is the 13-valent PCV-13 (table 2.5),[213-215] and this vaccine replaced PCV-7 in UK vaccination schedules in April 2010. Crucially, this new vaccine contains serotypes 1 and 7F that are particularly associated with invasive disease, and serotypes 3 and 19A that have been associated with emergent complicated or higher severity CAP. One recent study has suggested that the inclusion of the additional six serotypes will increase the current coverage of serotypes in IPD in children from 4.5% to 79.1%.[129] However, no large scale trials have been performed in children to date using this vaccine.

Vaccination of adults with conjugate vaccines

A randomised controlled trial is currently underway in the Netherlands, vaccinating adults with PCV-13 in patients who have not received PPV (CAPITA).[216] This trial will use IPD and pneumococcal CAP as outcome measures, and crucially will use the detection of urinary antigen to have a much higher sensitivity for detecting pneumococcal CAP. A barrier to the widespread vaccination of older adults with a conjugate vaccine is the presence of high rates of PPV use. As previously mentioned, repeat vaccination of adults leads to lower antibody rises, and this may blunt the response to conjugate vaccination in adults who have previously received PPV.[217] CAPITA circumvents this problem as few older adults in the Netherlands are

vaccinated with PPV, but use of a conjugate vaccine in adults in the UK may be more problematic for this reason.

Conclusions

Pneumococcal CAP is a common cause of mortality and morbidity worldwide, and an effective vaccination policy for children is reducing disease in both children and adults. Different pneumococcal serotypes show substantial phenotypic differences. However, a shift in serotype distribution has been seen following the introduction of the conjugate vaccines which may have implications for the spectrum of disease in both adults and children.

Chapter 3: Diagnosis, assessment and management

“A hundred years ago the treatment of pneumonia was heroic…he was therefore bled, purged, starved, blistered and doped with opium.”

“Diseases of the Chest”, Dr Robert Coope (1944)

Introduction

This chapter reviews the literature concerning the experience of CAP at the "front door" for the hospital physician, which is relevant to studies contained within the later chapters. It principally addresses:

- The most appropriate methods for confirming the microbiological diagnosis of pneumococcal CAP;
- A review of severity assessment, including novel assessment tools;
- The role of timing of interventions in the admission process and the effect on outcome;
- A review of the commonly used outcome measures in CAP.

Microbiological aetiology and diagnostic techniques

Rationale for clinical microbiology

Knowing the infectious agent responsible for an episode of CAP is useful for a number of reasons:

- An accurate microbiological diagnosis may allow the physician to change the patient's antibiotic regimen from broad spectrum to a more targeted one.
- Microbial culture may enable identification of antibiotic resistance, which can allow the clinician to change an ineffective antibiotic regimen. Narrowing the antibiotic spectrum reduces the volume of antibiotic usage with advantageous consequences on the wider microbiological ecology.
- Local up-to-date microbiologically relevant epidemiological data can help guide the selection of empirical antibiotics for CAP.
- Certain pathogens such as *Legionella pneumophila* have public health implications.

A summary of the most commonly used microbiological tests is shown in table 3.1. The consensus in the UK is that initial antibiotic regimens should consist of beta-lactam monotherapy (such as amoxicillin) for CAP of low severity, and a beta-lactam plus macrolide (such as clarithromycin) dual therapy for moderate and high severity CAP.[1] Beta-lactam antibiotics have good activity against *Streptococcus pneumoniae*, and penicillin non-susceptibility rates in the UK are currently below 10%,[102] lower than those found in many other parts of the world.[218-221] The addition of an empirical macrolide to the regimen is felt to be necessary to cover *Legionella pneumophila*, an atypical pathogen which despite being of relatively low incidence (around 5%),[7, 24, 222] is not susceptible to penicillin and can cause severe disease.

Technique	Sensitivity (%)	Specificity (%)	References
Streptococcus pneumoniae			
Blood culture	8	100	24, 223
Sputum culture and Gram stain	15-100	15-100	224-227
Urinary antigen	65-82	82-97	228-231
RT-PCR	61	87	232
Legionella pneumophila			
Urinary antigen	76-94	100	233, 234
RT-PCR	86-92	95-98	235
Serology	63-82	-	236
Chlamydophila pneumoniae			
Serology	87-100	85-97	237, 238
Mycoplasma pneumoniae			
Serology	74	90	239

RT: reverse transcription; PCR: polymerase chain reaction.

Table 3.1. A summary of the microbiological investigations used for the diagnosis of community-acquired pneumonia.

In the majority of CAP managed in primary care microbiological aetiology is neither sought nor clinically required, as the majority of CAP within this setting is of low severity, has a low mortality, and will resolve with empirical antibiotics.[240] In the hospital setting however a definitive microbiological diagnosis may help focus the antibiotic regimen (in particular, to substantially narrow the spectrum of antibiotic cover), and thereby improve length of stay or rate of adverse outcomes.

Such improvements in clinical outcomes have not been adequately tested. In one trial where pathogen-directed antibiotic treatment was compared with empirical broad-spectrum treatment, no benefit in length of stay or adverse outcome was observed,[20] although there was significantly lower reporting of adverse events in the pathogen-directed treatment arm. A further study randomised 177 hospitalised patients to receive targeted (based on microbiological diagnosis with pneumococcal urinary pneumococcal antigen testing; see later) or empirical oral antibiotic treatment following an initial course of broad spectrum intravenous antibiotics.[241] Reductions in antibiotic use were seen in the active arm, but no benefit in outcome was demonstrated, although the trial was small; antibiotic changes were possible in only 25/88 patients in the targeted group. Crucially a statistically significant rise in the clinical relapse rate was observed in the targeted antibiotic group. However, the numbers of patients within this study were small (there were only six relapses in the entire cohort), and therefore the results should be interpreted with caution. Additionally, all patients received the same broad spectrum antibiotic regimen on admission, and so antibiotics in the targeted group only reflected the change to oral antibiotics following attainment of clinical stability.

Therefore it remains to be seen whether antibiotic strategies based on microbiological diagnosis benefit patients; studies so far have shown reduced broad spectrum antibiotic use but have failed to demonstrate benefit in terms of patient outcome. Further work in this area is required.

Culture-based techniques

Blood cultures

Blood cultures are mandatory in most forms of sepsis, in addition to culture of the relevant infected area, such as urine or stool. Culture provides not only the identity of the infecting organism (with a clearly high specificity), but also gives information on subtype and antibiotic sensitivities. However, the diagnostic yield of blood cultures in CAP is low. In one study looking at this issue, only 5.7% patients presenting with CAP had a positive blood culture, and in only 2.0% did this change subsequent management.[223] These findings were replicated by Abe and colleagues, who recorded only six cases of bacteraemia in 164 consecutive CAP cases (3.7%). Of these, two were felt to be due to other co-existing disease.[242] A third study estimated the rate of bacteraemia in a cohort admitted from ED at 4.5%.[243] These data have led to guidelines recommending the omission of blood cultures for low severity CAP in the absence of co-morbid disease.[1]

Respiratory tract samples

Sputum samples are relatively quick, cheap, and easy to obtain in many patients with CAP. However, there are numerous practical difficulties, such as a patient being unable to produce a sputum sample, sample contamination, and delays in transport to the microbiology laboratory for prompt analysis. In a recent study on the utility of sputum in the diagnosis of CAP,[224] only 36% of 116 patients were able to produce a sputum sample for a variety of reasons including unproductive cough efforts, weakness, and non-compliance. Of these samples, only 55% were judged to be microscopically valid as defined by numbers of epithelial cells and leucocytes in a low-power microscopic field. Gram's stain may be of greater clinical utility than culture, as results are available more quickly. The benefits of sputum culture and Gram's stain have been the source of much debate, as there is great heterogeneity amongst studies describing the sensitivity and specificity of these tests.[225] In a recent study of blood culture-proven pneumococcal CAP, sputum Gram's stain alone had a sensitivity

of 57%, and the combination of culture and Gram's stain a sensitivity of 79%, *as long as the sample was adequate*.[226] Antibiotic administration rapidly reduces the sensitivity of sputum culture.[226, 232] In contrast, sputum Gram's stain and culture have a very high specificity. A prospective study of 533 patients with CAP collected 210 good quality sputum samples, of which 175 provided a clinically useful predominantly single organism result. This study found that the specificity for pneumococcal CAP was 97%, and for *H. influenzae* CAP 99%.[227] Therefore sputum Gram's stain may be worth obtaining prior to antibiotic use in a clinical setting, as a positive result for these pathogens will secure a diagnosis; but is not sensitive enough to be used as a research tool.

Flexible fibreoptic bronchoscopy, especially in combination with quantitative bronchoalveolar lavage (BAL) or protected specimen brushes (PSB), is a powerful tool for obtaining respiratory microbiological samples, avoiding contamination with the upper respiratory tract flora. This technique also enables samples to be obtained in those patients without a productive cough. BAL is widely used for the diagnosis of CAP caused by *Pneumocystis jiroveci* or fungal pathogens in immunocompromised patients, and both BAL and PSB have been used to investigate the microbial aetiology of lung abscesses.[244, 245] One study in patients with CAP demonstrated an improvement in the microbiological diagnostic rate of 26% and 36% respectively for BAL and PSB over sputum cultures.[246] In the intubated patient, invasive respiratory samples are more readily obtainable, and also improve diagnostic yield.[247] However, these techniques are clearly not practical for a large scale CAP study.

Non-cultural techniques

Antigen testing

Culture techniques have an insufficient sensitivity for use in CAP research. However, antigenic components of the infecting organism can be detected in tissue samples and this may provide a rapid diagnostic tool, and greatly increase the proportion of CAP in which a microbiological diagnosis is made.

A commercial immunochromatographic membrane assay (ICT) is available, which detects the C-polysaccharide capsule component found in the all *Streptococcus pneumoniae* serotypes, usually from a urine specimen. In patients admitted with CAP, this test has a sensitivity of 65-75% and specificity of 94-100%,[228, 229] and is positive up to a few weeks after admission irrespective of antibiotic treatment.[230] The sensitivity of this assay is shown in table 3.2, and is clearly superior to culture-based techniques. The use of urinary antigen detection in combination with other diagnostic tests substantially increases the percentage of patients who receive a definitive microbiological diagnosis.[231, 248] Antigen testing has also been applied to sputum,[249] and pleural fluid,[250] both of which have been shown to increase the diagnostic yield. The test is not affected by HIV status.[251]

Study	N	Comparator	Sensitivity (%)	Specificity (%)
Boulware 2007 [251]	70	Sputum, blood	81	98
Briones 2006 [231]	911	Sputum, blood, BAL	81	80-99
Roson 2004 [229]	220	Sputum	65.9	100
Ishida 2004 [228]	349	Blood, sputum, pleural fluid	75.9	94
Smith 2003 [252]	107	Blood	82	97
Gutierrez 2003 [253]	493	Sputum, blood	70.4	90
Straalin 2003 [254]	215	Sputum, blood, nasopharynx; any line as positive	79	83
Straalin 2003 [254]	215	Sputum, blood, nasopharynx; strong line only	54	92

BAL: broncho-alveolar lavage.

Table 3.2. Published data on the efficacy of the Binax NOW® immunochromatographic assay for testing urine in patients with CAP.

Nucleic acid amplification techniques

There is a great heterogeneity within the literature with regards sensitivity and specificity of polymerase chain reaction (PCR), presumably reflecting the wide variety of different protocols and assays used. In one study examining the utility of PCR for pneumolysin DNA in blood samples from patients with bacteraemic pneumococcal CAP it was found to be positive in only 57% of patients and had a sensitivity of 21-45% depending on the assay used within this population.[255] Specificity was high, at 97-100%. A further study using PCR for *S. pneumoniae* from a variety of sites suggested that the test was inferior to existing microbiological techniques, with only 19/465 patients with CAP tested having a positive result [256]. In contrast, another study using pneumolysin gene PCR in serum of patients with CAP identified pneumococcal disease in 41/184 patients, compared with 7/184 who had positive pneumococcal blood cultures.[257] However, two patients with positive blood cultures were negative by PCR. Another paper looking at prospectively collected cases of both bacteraemic and non-bacteraemic CAP reported sensitivity and specificity for PCR of 55% and 81% respectively,[258] comparable to standard techniques for identifying pneumococcal disease. The most recent paper on this issue examined rapid real-time PCR assays for the detection of the genes for the pneumococcal antigens pneumolysin, Spn9802, and lytA in serum from patients with CAP, reporting sensitivities of 26%, 32% and 42% respectively.[259] A comparative study of serum PCR for the genes for pneumolysin and autolysin with urinary antigen for *S. pneumoniae* reported sensitivities of 53.5% and 88.1% respectively.[260] There are clearly a variety of non-standardised assays in use, and until reliably high sensitivities can be produced blood or serum PCR for pneumococcal disease will not become established in the clinical environment.

PCR of respiratory secretions is desirable as it can potentially provide a sensitive and non-invasive rapid diagnosis. It is of particular advantage for the atypical pathogens, which are difficult to culture or lack an antigen test. However, as discussed in chapter 2, a proportion of healthy adults demonstrate nasopharyngeal carriage of

pneumococci,[49, 53, 54, 232, 256] and therefore PCR techniques may not distinguish pneumococcal disease from carriage. However, quantitative PCR might enable the investigator to assess bacterial load, which would be higher in pneumococcal disease compared with carriage. Applying real-time quantitative PCR for *S. pneumoniae* to induced sputum samples improves diagnostic rate over sputum culture alone, especially in those patients who have had antibiotic treatment prior to hospital admission,[261] and increases the proportion of all-cause CAP for whom a microbiological diagnosis is made to up to 89%.[25] Quantitative sputum PCR for *S. pneumoniae* has also been tested in the emergency department setting, showing favourable diagnostic rates as compared with convention culture methods, but with results available much more rapidly.[262] PCR for the pneumolysin gene has been applied to lower respiratory tract samples obtained bronchoscopically, but in order to obtain a specificity of more than 90%, sensitivity of the assay dropped to only 53%, significantly less than the urinary antigen assay.[259] Applying quantitative PCR for the gene target *lytA* to blood samples of 45 CAP patients allowed quantification of "blood DNA load", which was detected in 67% of patients with pneumococcal CAP,[263] levels of DNA load were also correlated with inflammatory response as measured by C-reactive protein and white cell count.

In summary, PCR of respiratory tract samples for pneumococcus seems to be a sensitive and rapid method for the diagnosis of certain CAP pathogens, but many protocols are in use, and techniques have yet to be internationally standardised. Therefore it has not entered routine use on most hospital laboratories. Further work in this area seems warranted.

Summary

A variety of diagnostic techniques are available for identifying *S. pneumoniae* in patients with CAP. The most sensitive test to have entered routine clinical use is the ICT assay (principally for urine samples) which out-performs standard culture techniques.

Severity assessment

Severity assessment is a key stage in the admission process, informing treatment and site of care decisions.[1, 264] A number of severity scores have been developed to aid the physicians' clinical judgement and help to stratify patients for a variety of adverse outcomes.[265] In addition, a number of other independent markers of disease severity have been assessed in the literature that may contribute to the efficacy of severity assessment.

Severity scores

Pneumonia severity index

The Pneumonia Severity Index (PSI) was the first rigorously derived severity score for CAP that entered widespread use. Fine and colleagues derived the rule from a retrospectively analysed database of 14,199 patients admitted to hospital with CAP in the USA, and validated it in an independent cohort of over 40,000 more inpatients and outpatients.[266] Easily obtainable, relevant potential variables associated with 30-day mortality on univariate analysis were identified, and twenty variables achieved significance in predicting 30-day mortality using logistic regression analysis. The coefficients from the logistic regression model were subsequently used to generate points weighting for each predictor variable, allowing a score to be generated reflecting the probability of death 30 days following admission for each patient. These scores allow separation into five risk classes (I-V).

The PSI has been validated in numerous international cohorts (table 3.3). The most widely used statistical tool to assess the efficacy of severity scores is the receiver-operating characteristic (ROC) curve, which is a plot of one minus specificity against sensitivity of a test for a given outcome. The area under the curve (AUC) of each plot gives a measure of the accuracy of a particular tool in predicting the relevant outcome.[267] A test that perfectly predicts the desired outcome will have an AUC of 1, whereas a test with no predictive value will have an AUC of 0.5. A value of 0.8 or

more is generally held to be the threshold above which a test predicts the desired outcome with sufficient strength. As can be seen in table 3.3, studies generate an AUC in predicting 30-day mortality for the PSI of between 0.72 and 0.89, with the majority of values falling above 0.8.

Paper	N	Country	ROC AUC
España 2010 [268]	1501	Spain	0.81
Menendez 2009 [269]	453	Spain	0.81
Phua 2009 [270]	1242	Singapore	0.86
Chalmers 2009 [271]	314	UK	0.79
Feldman 2009 [272]	742	South Africa	0.721
Schuetz 2008 [273]	371	Switzerland	0.72
Renaud 2007 [274]	925/853	France/Spain	0.85-0.89
Tejera 2007 [275]	226	Spain	0.752
Man 2007 [276]	1016	Hong Kong	0.736
Spindler 2006 [277]	114	Sweden	0.85
Capelastegui 2006 [278]	1776	Spain	0.888
Buising 2006 [279]	392	Australia	0.82
Aujesky 2005 [280]	3181	USA	0.81

AUC: area under the curve; ROC: receiver-operating characteristic curve.

Table 3.3. Efficacy of PSI in different international cohorts.

Unfortunately the PSI has a number of problems which has prevented it becoming more widely used. As a 20-point, two stage score it is cumbersome to use, and is therefore difficult to implement in the setting of a busy acute medical area or emergency department. In addition, prediction is only made for 30-day mortality, rather than other outcomes of interest (such as admission to critical care or pneumonia-specific complications). This is relevant as it has been suggested that of patients admitted with CAP who die within 30 days, only 53% of mortality is directly attributable to CAP.[281] Therefore there is a need for both simpler clinical scoring systems and scores that predict other outcomes.

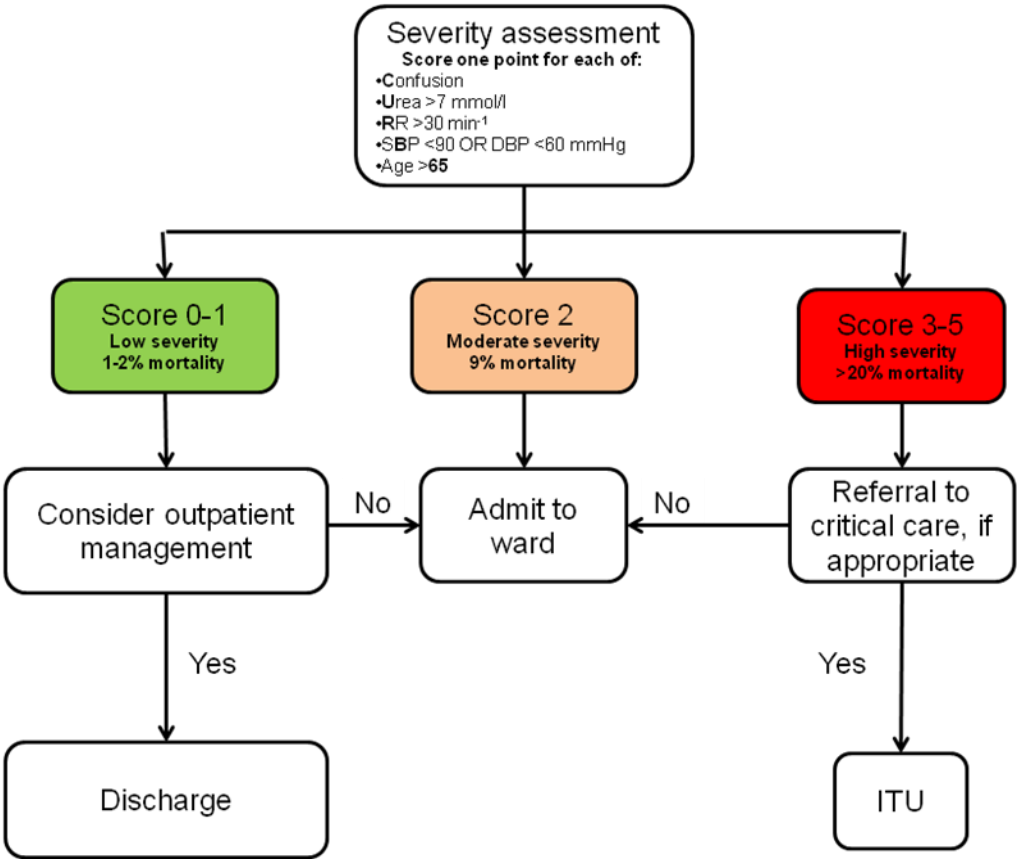
CURB-65 and CRB-65

These two scores have been developed with the aim of providing a simple tool for use in acute hospital areas and primary care, which accurately predicts not only those patients of low mortality and therefore who are suitable for management at home, but also those of moderate and high severity who require urgent hospital admission or access to critical care.

An initial investigation into severity assessment by the British Thoracic Society (BTS) using a prospectively collected cohort of 453 patients identified a number of variables associated with 30-day mortality on multivariate analysis,[282] including age, absence of chest pain, absence of vomiting, previous treatment with digoxin, tachypnoea, diastolic hypotension, confusion, low or high white cell counts, and raised blood urea levels. A patient with two out of three of respiratory rate ≥30, diastolic blood pressure ≤60mmHg and urea >7mmol/l had a 21-fold increase in 30-day mortality. Based on these data, three different short prediction rules were generated using three different statistical techniques. A rule comprising these three variables was validated in a second independent study.[283]

This was developed further by Neill and colleagues,[284] who collated four binary variables from these three previously generated rules into one modified prediction rule (mBTS), consisting of mental confusion, respiratory rate ≥30/minute, diastolic blood pressure ≤60mmHg, and urea >7mmol/l, and validated this on a separate patient cohort (n=316). This rule enabled patients to be divided into mild-moderate (<2 features) or severe (≥2 features) CAP based on 30-day mortality. The mBTS rule had a higher sensitivity for 30-day mortality than the three previous rules (95%) and retained a moderate specificity (71%). However, the stratification of patients into only two groups was limiting, and did not identify patients of low severity who might safely be discharged (or managed at home if seen in primary care).

The most recent iteration of this severity rule development in the UK consisted of a cohort of 1068 patients derived from 3 centres in the UK, Netherlands and New Zealand.[285] A randomly selected 80% of this cohort was used for derivation, with the remaining 20% being used as a validation data set. Using the mBTS rule as a starting point, twelve different variables were assessed on univariate analysis using Pearson's χ^2, of which ten showed a significant association with 30-day mortality. When the mBTS score ≥2 was entered as a single variable plus each of these variables into a backward logistic regression model, age ≥65 and serum albumin <30g/l were found to be independently significantly associated with 30-day mortality in addition to the four variables already contained within the mBTS rule. However, as albumin is not a routinely requested test for patients admitted with CAP, only age ≥65 was added to the mBTS rule. Thus five variables (figure 3.1) were incorporated into this new prediction rule, named CURB-65.



ITU: intensive therapy unit. Figure derived from Lim *et al*., 2003.[285]

Figure 3.1. Algorithm describing the role of CURB-65 in the admission process for pneumonia.

This score allowed stratification of patients into three severity groups of low, moderate and high severity CAP (figure 2.1). Each group predicts a different level of 30-day mortality, and therefore helps to inform management decisions including site of care and antibiotic decisions. It has been adopted by the BTS in their most recent guidelines as the severity assessment tool of choice in the UK.[1] CURB-65 has been validated in a variety of different international cohorts, with AUC on ROC curves of between 0.69 and 0.87, as summarised in table 3.4.

CRB-65 is an abbreviated version of CURB-65 that is intended for use in primary care as it omits the need to measure blood urea, a test not routinely available in the community. Its predictive ability as measured by the AUC of a ROC curve for 30-day mortality is similar to CURB-65 (table 3.5), and is recommended for use in primary care by the BTS.[1, 286] As CRB-65 also stratifies patients into three risk groups it can help to inform clinical judgement and guide management, as described in figure 3.2.

As previously discussed with the PSI, a criticism of these two severity scores is that they only predict 30-day mortality, which may not be the only outcome of interest or relevance to the attending clinician, as discussed in the previous chapter. In addition, fewer risk classes are present with lower severity CAP compared with PSI, which has led to claims that PSI is superior to CURB-65 in predicting those patients who may be suitable for management at home (which is what PSI was initially designed to do).[280]

Paper	N	Country	ROC AUC
España 2010 [268]	1501	Spain	0.78
Menendez 2009 [269]	453	Spain	0.82
Phua 2009 [270]	1242	Singapore	0.82
Feldman 2009 [272]	744	South Africa	0.736
Zuberi 2008 [287]	137	Pakistan	0.863
Schuetz 2008 [273]	371	Switzerland	0.69
Shindo 2008 [288]	329	Japan	0.835
Chalmers 2008 [289]	1007	UK	0.76
Barlow 2007 [290]	503	UK	0.78
Tejera 2007 [275]	226	Spain	0.784
Man 2007 [276]	1016	Hong Kong	0.733
Challen 2007 [291]	186	UK	0.788
Spindler 2006 [277]	114	Sweden	0.84
Buising 2006 [279]	392	Australia	0.82
Capelastegui 2006 [278]	1776	Spain	0.870
Aujesky 2005 [280]	3181	USA	0.76

AUC: area under the curve; ROC: receiver-operating characteristic curve.

Table 3.4. Efficacy of CURB-65 in different international cohorts.

Paper	n	Country	ROC AUC
Feldman 2009 [272]	744	South Africa	0.737
Menendez 2009 [269]	453	Spain	0.79
Schuetz 2008 [273]	371	Switzerland	0.66
Chalmers 2008 [289]	1007	UK	0.74
Zuberi 2008 [287]	137	Pakistan	0.835
Barlow 2007 [290]	503	UK	0.73
Man 2007 [276]	1016	Hong Kong	0.694
Schaaf 2007 [292]	105	Germany	0.845
Spindler 2006 [277]	114	Sweden	0.83
Bauer 2006 [293]	1343	Germany	0.785
Capelastegui 2006 [278]	1776	Spain	0.864

UK: United Kingdom; AUC: area under the curve; ROC: receiver-operating characteristic curve.

Table 3.5. Efficacy of CRB-65 in different international cohorts.

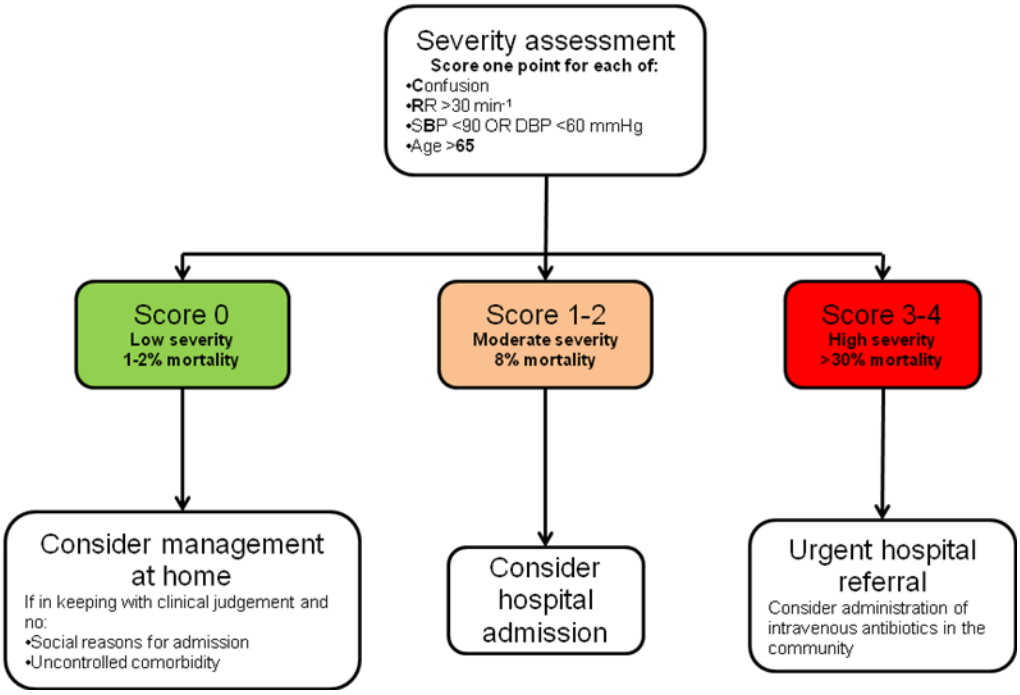


Figure derived from Lim *et al*., 2003.[285]

Figure 3.2. CRB-65 scoring and outpatient management of community-acquired pneumonia.

eCURB

The disadvantage of scores based on binary variables is that they artificially transform continuous variables, such as blood urea. Binary variables incorporate an arbitrary cut-off point, which improves ease of use in a clinical environment, but may be unrealistic; for example, a blood urea level of 7.1 should not be significantly more predictive of mortality than 7.0. In addition, this model does not take into account non-linear distributions of these variables. For example, a high urea is clearly predictive of mortality, but an abnormally low urea may also reflect malnutrition, and also put the patient at higher risk of death.

A more attractive model would be one which incorporated weighted continuous variables into a statistically derived and validated model. However, this could potentially reduce clinical utility as it would inevitably involve complex calculations that cannot be performed without the aid of a dedicated computer program. However, with the increasing presence of computer-based results reporting and clinical note writing available at the front door, it is reasonable to expect that a computer based severity scoring system is achievable.

Such a model has been derived based on the CURB-65 criteria using a lasso-penalized logistic regression model, with natural cubic splines with three knots applied to the urea, respiratory rate, blood pressure, and age elements (hereafter known as "eCURB"). This model was derived on 2076 patients from a computerised database in the USA,[294] and validated in a cohort from a previous Nottingham prospective CAP observational study.[24] This score showed an improvement of ROC AUC in the derivation cohort over binary CURB-65 from 0.82 to 0.87, and in the validation cohort from 0.80 to 0.85. A further advantage of using a computerised severity scoring tool is that rather than assigning a patient to a mortality risk category based on the score (low, moderate or high severity) eCURB gives a point estimate of mortality.

Other severity scores

PSI, CURB-65 and CRB-65 are the most widely validated and accepted standards internationally for predicting 30-day mortality in CAP. However, whilst increasing severity as measured by these rules may correlate with other outcomes,[278] they are less accurate at predicting complications,[295] need for mechanical ventilation,[296, 297] or critical care admission,[279, 298, 299] than 30-day mortality. Therefore a number of other severity scores have been developed to address these outcomes.

Identifying patients at risk of requiring admission to critical care is important as death from CAP is a far less common outcome in the younger population,[300] who often score inappropriately low on existing severity scores. This is in contrast to the older population with severe co-morbidity who represent the majority of admissions with CAP,[8, 9] but who may have less scope for therapeutic intervention. SMART-COP is an eight-point tool derived using a similar methodology to that described earlier.[296] The derivation cohort consisted of 882 patients with CAP admitted to hospital in Australia, and was validated in five other CAP cohorts totalling 7464 patients. The variables included in the final model were:

- Systolic blood pressure <90mmHg (two points)
- Multilobar chest radiograph involvement (one point)
- Albumin <35g/l (one point)
- Respiratory rate ≥25min^{-1} if age ≤50 years; ≥30min^{-1} if age >50 years (one point)
- Pulse ≥125min^{-1} (one point)
- New onset confusion (one point)
- Arterial partial pressure of oxygen (p_aO_2) <70mmHg, or capillary oxygen saturation (s_pO_2) ≤93% or p_aO_2:fraction of inspired oxygen (f_iO_2; P/F ratio) <333 if age ≤50 years; p_aO_2<60mmHg or s_pO_2 ≤93% or P/F ratio <333 if age >50 years (two points)
- Arterial pH <7.35 (two points)

This score may be interpreted as follows:

- Score 0-2: Low risk of mechanical ventilation or inotropic support
- Score 3-4: Moderate risk of mechanical ventilation or inotropic support
- Score 5-6: High risk of mechanical ventilation or inotropic support
- Score ≥7: Very high risk of mechanical ventilation or inotropic support

A version of this tool has also been developed omitting albumin, pH and p_aO_2 for use in primary care, where these investigations are not readily available (hereafter referred to as "SMRT-CO").

The AUC for this tool in predicting need for mechanical ventilation or inotropic support in this cohort was 0.87, in contrast to 0.67 for CURB-65 and 0.69 for PSI.[296] This reflects the increased importance this score places on physiological variables (especially oxygenation) compared with CURB-65 and PSI, with a lesser emphasis on patients' co-morbidity and age. These two latter variables if present make a patient less likely to be suitable for critical care admission. SMART-COP has been validated in only one independent cohort,[301] consisting of 335 patients aged less than 50 years. This confirmed the improved prognostic value for mechanical ventilation or inotropic support compared with CURB-65 or PSI (AUC 0.87 vs. 0.81 and 0.80 respectively).

The limitations of this score are as follows:

- It is yet to be as extensively validated as CURB-65 and PSI;
- It is substantially more complicated to calculate than CURB-65 or CRB-65, limiting its utility as a front-door assessment tool;
- Criteria for mechanical ventilation and inotropic support are not standardised between health systems, and therefore predictive accuracy will vary between countries such as the UK and USA.

A second score, SCAP, aims to develop a tool to predict severe CAP, as defined by any of the adverse outcomes of inpatient mortality, need for mechanical ventilation or shock.[268, 297] Using a similar methodology, a Spanish group derived a score that predicts any of these adverse outcomes with an AUC of 0.86 in the internal validation cohort, compared with 0.75 for CURB-65 and 0.79 for PSI.[297] However, when these three scores were applied to an external validation cohort the differences in AUC were only 0.72, 0.69 and 0.71 respectively. As is shown in table 3.6, SCAP principally adds measures of hypoxaemia from arterial blood gas analysis, multilobar involvement on chest radiograph and arterial pH to the CURB-65 criteria, whilst increasing the age threshold from 65 to 80 years. The same group deriving the score performed a validation study,[268] which extended the use of this score to predicting 30-day mortality, showing non-inferiority to CURB-65 and PSI. This score was also validated by a second group, and showed ROC AUCs of 0.746 and 0.760 for admission to critical care and mechanical ventilation respectively.[302]

The criticisms for this score are as follows:

- Arterial blood sampling is integral to the score; this test is only indicated in patients who are suspected to be severely hypoxaemic or at risk of severe metabolic derangement;[1]
- It remains to be widely validated in numerous international cohorts;
- It is more complicated to perform or remember than the much simpler CURB-65 and CRB-65.

Severe CAP is defined by any one of:

- Arterial pH <7.30
- Systolic blood pressure <90mmHg

OR

Any two of:

- Confusion
- Urea >30mg/dl
- Respiratory rate >30min^{-1}
- Multilobar or bilateral changes on chest radiograph
- p_aO_2<54kPa or p_aO_2/f_iO_2 ratio <250mmHg
- Age ≥80 years

p_aO_2: arterial partial pressure of oxygen; f_iO_2: fraction of inspired oxygen.

Table 3.6. The SCAP severity score.

The severity scores presented so far have been used to predict outcome in all patients with CAP. The PIRO (predisposition, insult, response, organ dysfunction) score was initially developed in a critical care setting to predict mortality from ventilator-associated pneumonia (VAP),[303] but was further refined for use in patients admitted to the ICU with CAP.[304] A cohort including 33 intensive care units and 529 adult patients with CAP identified eight prognostic variables:

- Co-morbidity (for example, chronic obstructive pulmonary disease)
- Age >70 years
- Multilobar changes on chest radiograph
- Shock
- Severe hypoxaemia
- Acute renal failure
- Bacteraemia
- Acute respiratory distress syndrome (ARDS)

This allowed stratification of patients admitted to critical care with CAP into 4 groups:

- Low (0-2 points
- Mild (3 points)
- High (4 points)
- Very high (5-8 points)

Mild, high and very high risk patients were associated with hazard ratios for 28-day mortality of 1.8, 3.1 and 6.3 respectively. The AUC for the ROC curve in predicting 28-day mortality was 0.88. However, this score has not yet been validated in an external cohort. It also does not facilitate changes in management, as adjunctive therapies beyond antibiotics and supportive therapy have little evidence base. Thus stratifying patients already in critical care would currently seem to have little additional value.

Oxygenation

Assessment of oxygenation is essential on admission to hospital,[1] and is being increasingly incorporated into management in primary care.[305] Oxygenation can be estimated in several different ways. Measurement of capillary oxygen saturation (s_pO_2) may be performed rapidly and non-invasively with a pulse oximeter, which utilises the differing spectral characteristics of oxy- and deoxy-haemoglobin. The partial pressure of arterial oxygen (p_aO_2) may be measured via arterial blood sampling, a significantly more invasive test.

A p_aO_2 of less than 8kPa was found to be independently associated with increased 30-day mortality in a subsequent analysis of the cohort used by Fine and colleagues to derive PSI,[266] showing a hazard ratio for pneumonia-related mortality of 1.99.[281] A subsequent cohort of 533 CAP patients from Spain calculated an OR for mortality of 4.6 for patients admitted with p_aO2 <8kPa.[306] España and colleagues found that a p_aO_2:f_iO_2 (P/F) ratio of <250 had an OR of 6.5 for inpatient death, mechanical ventilation or shock. Mortality has also been associated with low P/F ratios, and failure of improvement of P/F ratios with 48 hours.[307] Sanz and colleagues analysed a cohort of low severity CAP (PSI-III), and found that hypoxaemia (P/F ratio <300) was more prevalent in the elderly and those with significant co-morbidity.[308] In addition, hypoxaemic patients had a significantly longer hospital length of stay (LOS), and higher rate of admission to critical care (CC).

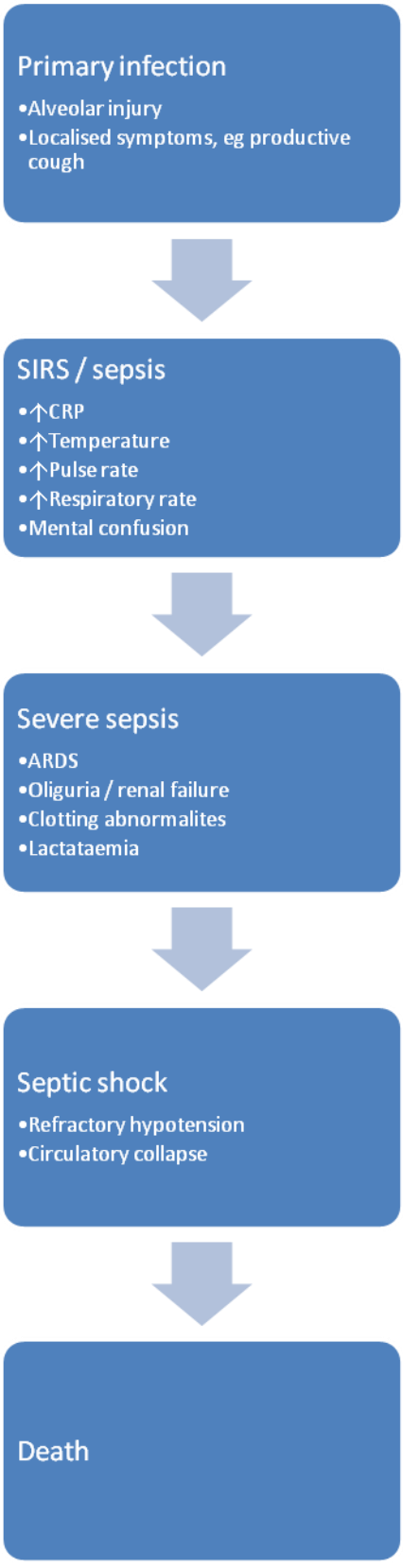
As previously mentioned, arterial blood gas analysis is an invasive test, and is not appropriate for every patient admitted with CAP. Findings from a US CAP cohort demonstrated an association between low s_pO_2 levels measured on admission and a higher 30-day mortality and incidence of admission to critical care.[309] Low s_pO_2 in the emergency department (ED) has been shown to significantly alter physician practice, including treatment, investigation and admission decisions,[310] and delays in oxygen assessment may result in delays in receiving antibiotics and higher mortality.[311]

Studies deriving pneumonia severity scores as described above have found hypoxaemia to be an independent predictor of mortality on univariate analysis,[24, 266, 296, 297] but of the two most commonly used severity scores, one (CURB-65) does not contain a measure of oxygenation, and the other (PSI) places relatively low weighting overall in the prediction of mortality. Indeed, only those scores that involve prediction of critical care admission rely to any great extent on hypoxaemia (SMART-COP and SCAP). This at first seems counter-intuitive. However, hypoxaemia seems to be different from variables such as blood pressure, mental confusion and respiratory rate which are closely linked to systemic disease and sepsis and therefore mortality. Hypoxaemia is a disease- and organ-specific measure, primarily of the level of shunt within the lungs. Physiological variables such as pulse, blood pressure and respiratory rate are unaffected by substantial hypoxaemia in healthy volunteers,[312] and correction of hypoxaemia has no influence on outcome either in a post-operative setting,[313] or in moderately hypoxaemic patients with CAP treated with continuous positive airways pressure (CPAP).[314] This may reflect the oxygen dissociation curve, which suggests that oxygen delivery to the tissues is only compromised at levels of S_pO_2 that are far lower than those associated with hypoxaemia as recognised within current practice. Therefore it may not be hypoxaemia *per se* that contributes to mortality, but that low s_pO_2 levels allow identification of the sub-group of patients who have severe single organ disease that falls short of influencing the sepsis-driven variables identified by most current severity scores. Hypoxaemia is however a major criterion for admission to critical care and ventilator support, explaining its use in predicting these outcomes.

In summary, the precise role of oxygenation assessment in conjunction with existing severity scoring is unknown. Oxygenation seems to be vital primarily to identify those hypoxaemic patients who would benefit from critical care admission rather than as a tool to predict 30-day mortality.

Antibiotic timing

That antibiotics are mandatory in confirmed CAP is not in question, but the timing of antibiotic delivery on arrival to hospital has generated substantial debate in recent years. Intuitively it would seem that the earlier antibiotics are delivered the better the outcome. Houck and colleagues have proposed the concept of the evolution of CAP as a progression through a sequence of states (figure 3.3), where antibiotic delivery is required as soon as possible in order to interrupt this progression.[315] This concept is supported by Kumar and colleagues, who investigated the progression of sepsis using a mouse model of *Escherichia coli* infection.[316] This study suggested that the earlier along this sequence that the mice were treated with antibiotics, the lower the 96-hour mortality. In addition, there was a "critical inflection point" for antibiotic delivery; in mice treated 12 hours after infection 96-hour mortality was 13%, compared with 80% for mice treated at 15 hours. There was no difference in mortality between mice treated at 0, 6 or 12 hours after infection respectively. This work is supported by two retrospective studies of patients with bacteraemic pneumococcal CAP (step two to three in the proposed sequence in figure 3.3), both of which show a strong mortality benefit to antibiotic delivery within 4 hours of admission.[317, 318]



SIRS: systemic inflammatory immune response; CRP: C-reactive protein; ARDS: acute respiratory distress syndrome.

Figure 3.3. The concept of progression in CAP and sepsis.

This biological plausibility of early antibiotic delivery providing a mortality benefit in CAP has been challenged. Symptoms of CAP have often been present for several days prior to presentation to hospital,[319] and therefore it is difficult to see in patients *who are not critically ill* how a few hours delay may make a significant difference to outcome. Additionally, antibiotics do not act instantaneously; although penicillin is bacteriocidal, four hours after application *in vitro* over 50% of bacteria may remain viable,[320] a figure which may be much higher *in vivo*.

The data on timing of antibiotics in CAP are similarly conflicting. Short time to first antibiotic dose (TFA) for patients hospitalised with CAP was associated with a lower mortality in two large database studies. In the first, a cohort of 14,069 patients aged more than 65 years was retrospectively analysed.[321] Delivery of antibiotics within eight hours of presentation was associated with an odds ratio of 0.85 for 30-day mortality. However, the demographic parameters of patients with TFA greater or less than eight hours were not presented, leading to the possibility of unmatched comparator groups. The second study retrospectively examined a cohort of 18,209 Medicare adult CAP cases.[315] The investigators found a statistically significant odds ratio of 0.90 between patients with a TFA greater or less than four hours, and 0.83 with a TFA greater or less than eight hours.

There were several major limitations to these studies. The first is that both were retrospective studies, with all the limitations such a study design imposes. Secondly, in both studies, patients treated within two hours of admission paradoxically had significantly *higher* mortality rates. Third, in only the second study were the clinical characteristics of groups with a TFA greater or less than four hours compared, showing that a higher proportion of patients in the TFA less than four hours group had vital signs abnormalities consistent with CAP or sepsis, such as hypoxaemia and tachypnoea. In contrast, patients in the TFA greater than four hours group were more likely to present with significant co-morbidity and mental confusion. This suggests that

some of the differences seen in these cohorts may have been due to difficulties in diagnosis delaying antibiotic delivery; that is to say, patients who present with a "clinically obvious" CAP receive treatment earlier. This finding has been explored by Waterer and colleagues using a prospectively collected cohort of CAP patients.[322] This study was much smaller than the studies previously described (n=451), and was underpowered to detect a statistically significant mortality difference by antibiotic timing. However, what this study does add is confirmation that factors such as absence of fever, mental confusion and absence of hypoxia strongly predict a longer TFA, thereby confounding any difference in mortality. A second small retrospective study reported initial potential diagnostic uncertainty in 19/86 (22%) of patients given a diagnosis of CAP, and the presence of this uncertainty was associated with a prolonged TFA.[323]

One prospective study has shown a benefit to early antibiotic delivery and reduced hospital length of stay.[324] However, several smaller prospective studies have been unable to replicate the mortality benefit seen with early antibiotic delivery, possibly due to lack of power.[319, 325-328] In addition, following the application of a "four hour rule" to antibiotic delivery for CAP in the US, reports emerged that the resulting time pressures increased the proportion of patients incorrectly diagnosed with CAP in the emergency department from 21% to 29%, and resulted in deteriorating antibiotic stewardship,[329] a finding replicated elsewhere.[330]

In summary, antibiotic delivery as early as possible to improve outcome is biologically plausible, evidenced based, and therefore desirable in those patients who have severe sepsis or septic shock. However, implementing this as a policy for all CAP patients and relegating the importance of preceding treatment with diagnosis, especially in those patients who are not ill, may lead to poor antibiotic stewardship, increased misdiagnosis rates and antibiotic-associated complications, and a resulting poorer standard of care.

Outcome

There is debate concerning the most appropriate way to measure outcome for patients with CAP. A discussion of the various possible outcome measures is presented below to understand why particular outcomes measures have been used later in this thesis.

Mortality

Mortality in the hospitalised population is well described. The 30-day mortality rates for previous major CAP cohort and database studies are shown in table 3.7. Whilst 30-day mortality is an important and well documented outcome in CAP, it is influenced by a number of different factors apart from the disease process itself. Mortensen and colleagues suggested that mortality is only pneumonia-related in 53% of cases, and co-morbidities such as malignancy or cardio-respiratory disease were responsible for a large proportion of deaths.[281] Mortality also does not provide information on the outcome of CAP of low to moderate severity, responsible for around two thirds of disease,[285] which has a low mortality. Therefore a number of studies have focused on other clinical outcomes.

Study	Country	30-day mortality,% (n)
Cilloniz 2011 [18]	Spain	7 (1463)
Espana 2010 [268]	Spain	10.9 (1501)
Ewig 2009 [9]	Germany	13.7-14.4 (388406)
Schuetz 2008 [273]	Switzerland	11 (371)
Garau 2008 [331]	Spain	8.7 (3233)
Chalmers 2008 [332]	Scotland	9.6 (570)
Menendez 2008 [333]	Spain	6.8 (453)
Charles 2008 [296]	Australia	5.7 (882)
Zuberi 2008 [287]	Pakistan	13.1 (137)
Tejera 2007 [275]	Spain	12.4 (226)
Man 2007 [276]	Hong Kong	8.6 (1016)
Buising 2006 [279]	Australia	9.4 (392)
de Roux 2006 [334]	Spain	10 (1511)
Colice 2004 [15]	USA	9.1 (1257)
Basi 2004 [335]	Canada	9.2 (1795)
Lim 2003 [285]	UK/Netherlands/NZ	9 (1068)
Roson 2001 [306]	Spain	10 (533)
Marrie 1989 [336]	Canada	21 (719)
British Thoracic Society 1987 [282]	UK	5.7 (453)

UK: United Kingdom; NZ: New Zealand; USA: United States of America.

Table 3.7. The range of estimates for 30-day mortality for adults hospitalised with CAP.

The discharge decision and length of hospital stay

Following a period of admission for CAP, the discharge decision may be influenced by a number of factors. Adverse social circumstances, clinical judgement, persistent symptoms, and patient preference may delay discharge beyond objective clinical and physiological CAP resolution. The discharge decision is particularly relevant for patients with non-severe CAP, who have a low mortality and therefore may be suitable to be managed at home or after a short inpatient stay.[266, 285] Only a small proportion of CAP is managed in hospital,[7] but this fraction accounts for the majority of the financial burden from this disease.[13, 14] Outpatient management of non-severe CAP is as safe and effective as hospitalisation,[337, 338] and patients often prefer outpatient to inpatient treatment.[339-342]

Clinical stability

Halm and colleagues were the first to generate data on the time course of the clinical resolution of CAP, and postulated five physiological and two other variables that should be attained prior to discharge (table 3.8).[343] This concept of "clinical stability" was reached at a median of three days after admission (six days for severe CAP), and correlated with CAP severity. In addition, once clinical stability had been reached the incidence of subsequent deterioration requiring CC admission was markedly reduced to below 1%. Of patients discharged from hospital with at least one or two clinical instabilities, 13.7% and 46.2% respectively died or were readmitted at 30 days compared with 10.7% of those with no instabilities.[344] One or more clinical instabilities on discharge were associated with death (adjusted OR 2.1), readmission (OR 1.5), and failure to return to normal activities (OR 1.5) within 30 days of discharge. International guidelines have adopted these criteria, stating that resolution of these parameters is necessary prior to discharge.[264] Other studies estimating time to clinical stability (TCS) have suggested a mean of 3.19-3.26 days,[326] and a median of four days.[345]

Parameter	Value
Systolic blood pressure	≥90 mmHg
Heart rate	≤100 min^{-1}
Oxygen saturation	≥90% on air, or the same as pre-admission
Respiratory rate	≤24 min^{-1}
Temperature	≤37.8°C
Mental confusion	Absent
Oral intake	Normal

Table 3.8. The seven factors defining clinical stability.

Symptom scores

Use of a symptom score as an outcome measure in studies of CAP has several advantages. A continuous variable such as a symptom score may allow more subtle influences on outcome to be detected than a categorical variable such as 30-day mortality. It also may allow better estimation of the impact of an intervention in patients with low severity CAP, a group which by definition have a low rate of adverse outcomes.

Symptoms may persist up to six months after clinical and radiological resolution,[346-348] and persist beyond "clinical cure" as rated by physicians.[349] Respiratory symptoms and quality of life (QOL) are rarely reported in CAP studies, despite being in many ways the most significant patient-centred outcomes. Scores based on QOL (predominantly the short form 36, (SF-36)) have been used as outcome measures in CAP clinical trials,[350, 351] but are clearly not specific to CAP. El Moussaoui and colleagues developed a clinical score (the "CAP score") based on an eight part questionnaire examining the symptoms of breathlessness, cough, and sputum in 67 hospitalised patients (appendix 2).[352] Scores were divided into respiratory and general well-being sections, and were measured at admission, days three, seven, ten, 14 and follow up at six weeks. Scores improved during follow-up and deteriorated in the event of clinical failure, and correlated with other clinical relevant variables such as inflammatory and physiological markers. In a follow up study, symptom scores had largely returned to normal within six months.[348] This score is yet to be validated in an external cohort.

A second symptom score ("CAP-sym") was developed by Lamping and colleagues in 33 patients, and validated on 556 patients.[353] This score consists of 18 questions, many of which are not specific to CAP (such as gastrointestinal disturbance, difficulty thinking and concentrating, and headache). However, the score correlated with clinical

cure rates within the study and had similar responsiveness to the score developed by el Moussaoui and colleagues.

Length of hospital stay

Intuitively, LOS is a surrogate measure for the clinical disease course and time to clinical stability in hospital following institution of treatment, and therefore a measure of disease severity and treatment efficacy. It is easy to measure, applicable to all hospitalised survivors with CAP, and is a useful measure in those patients with low severity CAP as a quality indicator, as this group should always be considered for early outpatient management.[341, 342] The majority of the financial cost of pneumonia to healthcare institutions is related to the number of hospital bed-days occupied.[13, 14, 354] Typical LOS in some large CAP cohorts is reported in Table 3.9. The disadvantage to using LOS as an outcome measure is that a variety of factors cause delays in discharge beyond the time taken to reach physiological stability.

Study	Country	Median LOS (days)
Garde 2008 [355]	Netherlands	10
Garau 2008 [331]	Spain	9
Barlow 2007 [328]	UK	5
Huang 2006 [356]	Canada	6
Menendez 2003 [357]	Spain	9
Rifkin 2002 [358]	USA	5
Lim 2001 [24]	UK	7
Dedier 2001 [327]	USA	4
Feagan 2000 [359]	Canada	7
Fine 1997 [266]	USA	7

LOS: length of hospital stay; UK: United Kingdom; USA: United States of America.

Table 3.9. The range of estimates for median length of hospital stay for adults hospitalised with CAP.

Delays to discharge

The times quoted for TCS are substantially shorter than those quoted for LOS, and significant variability in LOS has been demonstrated between different hospitals.[360, 361] In a questionnaire distributed to hospital clinicians in the US, four factors were identified that were thought to delay discharge in clinically stable patients:[362]

- Obtaining a diagnosis;
- Treating co-morbidity;
- Completing a course of antibiotics;
- Arranging long-term social care.

Laing and colleagues compared the discharge of patients in two similar hospitals in New Zealand, finding that main influence on the different LOS between the two hospitals was duration of intravenous therapy, with similar presenting pneumonia severity as measured by PSI.[363] A small study (n=31) looking at the disparity between LOS and TCS identified a measure of mobility and balance, the HABAM score, as a significant predictor of discharge delay after clinical stability.[364] A randomised controlled trial by Marrie and colleagues suggested that use of a CAP clinical pathway reduced the admission rate for patients with low severity CAP, and reduced LOS for those admitted, with no increase in adverse outcome,[351] a finding replicated elsewhere,[365] suggesting that physician practice is a key determinate of LOS. Finally, pre-admission functional status and significant co-morbidity have both been found to be independently associated with longer LOS.[356]

The discharge decision is therefore affected by a combination of physiological parameters, physician judgement (informed by guidelines, severity scores and experience), and clinical factors unrelated to the admission episode such as co-morbidity and functional status. These factors all reduce the utility of LOS as an outcome measure in CAP.

Need for critical care

30-day mortality for CAP in young patients is low, and as such this group is often overlooked when consideration is made of mortality alone. A number of studies have attempted to combine one or more outcomes, typically 30–day mortality and requirement for mechanical ventilation or inotropic support.[268, 297] This is of interest clinically as it allows a more robust definition and potential prediction of "severe CAP" defined in terms other than mortality alone. The incidence of mechanical ventilation for patients with CAP is summarised in table 3.10 below.

However, using CC admission, need for inotropes or need for mechanical ventilation as outcome measures reflects the subjective nature of these interventions. For example, the rate of admission to CC in the USA is higher across all diseases than in the UK due to differences in resource allocation and remuneration for health care, and admission criteria for CC are poorly standardised within the UK, let alone internationally.

Summary

In summary, there is no "ideal" way to measure outcome in CAP. For this reason, outcome is best summarised either by describing all of the possible outcomes, or describing outcome in a sub-population of patients admitted with CAP.

Study	Country	Proportion MV (n)
Singanayagam 2009 [366]	UK	7.8% (1050)
Garau 2008 [331]	Spain	3.1% (3233)
Charles 2008 [296]	Australia	4.6% (862)
Menendez 2008 [333]	Spain	6.4% (453)
Man 2007 [276]	Hong Kong	2.5% (1016)
Buising 2006 [279]	Australia	5.8% (3920)
Capelastegui 2006 [278]	Spain	1.6% (1100)
Roson 2001 [306]	Spain	5.6% (533)

UK: United Kingdom; MV: mechanical ventilation.

Table 3.10. The range of estimates for need for mechanical ventilation for adults hospitalised with CAP.

Chapter 4: Study of community-acquired pneumonia in adults 2

“What happens in any infection must depend on the seed and the soil – the invading power of the organism and the resistance of the host.”

“Diseases of the Chest”, Dr Robert Coope (1944)

Introduction

Chapters 2 and 3 have highlighted the current issues surrounding the prevention and treatment of pneumococcal CAP following the introduction of PCV-7. This chapter describes the study designed to address these outstanding issues.

The current evidence base

In order to comment on vaccine efficacy via a potential "herd immunity" effect and to inform future vaccine development, it is necessary to know the distribution of pneumococcal serotypes causing CAP in the adult UK population. Studies undertaken to date on pneumococcal serotype distribution are flawed for a number of reasons:

1. The majority of studies define pneumococcal serotype in cohorts of patients with IPD. This group comprises several non-CAP manifestations of pneumococcal disease, including meningitis, and septicaemia. The rates of these different manifestations are often reported within IPD studies (for example, in a study by Harboe and colleagues meningitis accounted for 14.6% of cases,[105] and in a similar study by Chiba and colleagues, for 17.5% cases,[109] but serotypes only reported for all-cause IPD).
2. The majority of studies are retrospective in nature and the diagnosis of CAP is therefore determined by retrospective disease coding rather than prospective clinical and radiological diagnosis. This is due to the relatively low frequency of bacteraemia with CAP (see point 3).
3. The studies to date have universally determined serotype from a cultured invasive sample (sputum, blood or pleural fluid) using the Quellung reaction.[367] As discussed in chapter 3, these methods have a low sensitivity for pneumococcal disease, and hence do not reflect the majority of the burden of pneumococcal CAP seen in UK hospitals.
4. Different serotypes have different invasive potential. For example, serotype 1 is thought to be highly invasive, and may therefore be over-represented in cohorts of

IPD compared to less invasive serotypes. As we have seen in previous chapters, invasiveness inversely correlates with adverse outcome, and therefore an under-representation of serotypes with low invasiveness in published cohorts may lead to the prevalence of these serotypes being underestimated, and a larger proportion of this potentially severe disease being missed.

5. Due to the relatively recent introduction of PCV-7 to infant immunisation schedules in the UK, no studies have been published to date including UK patients in the post-vaccination period.

Furthermore, as described in chapter 3, there are a number of outstanding questions surrounding the processes of care for adults admitted with CAP, and their influence on outcome. These include:

1. What is the role of symptom scores for assessing outcome?
2. How does oxygenation status help with assessment?
3. Does the multitude of severity scores remain valid in a modern UK cohort given the changing admission characteristics of CAP?
4. Does the timing of specific interventions, such as first antibiotic or chest radiograph, influence outcome?
5. What is the role of early senior respiratory specialist intervention in the management of CAP?

Broad objectives of the studies contained within this thesis

In order to improve outcomes in CAP, studies are required to address the questions highlighted above:

a) There is a need to prospectively gather information on the pneumococcal serotypes in invasive *and* non-invasive pneumococcal CAP in the adult UK population following the introduction of PCV-7 and PCV-13. This will provide information on what serotypes are prevalent, monitor changes in this serotype

distribution in the years following the introduction of these vaccines, and link any serotype shift to a potential change in the serotype-specific clinical features and outcomes of adults admitted with CAP. Such data would also inform pneumococcal vaccine research, particularly with respect to which serotypes it might be prudent to include within newer conjugate vaccines.

b) There is a need to clarify the precise role of current processes of care for adults admitted with CAP including oxygenation assessment, severity and symptom scoring, timing of specific diagnostic and treatment intervention, and utility of review by senior respiratory clinicians. This will enhance the front-door assessment and management of these patients, and potentially improve outcome.

Methods

Considered study methodologies

A variety of methods have been considered. The aims of the study are clearly observational, as the outcomes (serotype distribution, clinical features, and outcome of invasive and non-invasive CAP) are unknown. This means that controlled experimental research methods (such as a randomised controlled trial) are impractical. As we are interested in the evolution of disease and patients over a period of time, a longitudinal rather than cross-sectional study is the best method to approach the questions outlined above. A prospective observational study allows many potential clinical associations or risk factors to be gathered, minimising recall bias, and is thus a superior methodology to a retrospective study.

Once a cohort has been defined and recruited over a period of time a method is required for the purposes of determining clinical differences between serotypes. The nested case-control study methodology is essentially a traditional case-control study which is performed within a defined cohort.[368] The advantages of this method are that the cases are from the same population as the controls, and as data are collected prospectively there is no danger of recall bias, as with traditional case-control studies.

Setting

For the proposed prospective observational study the setting is the population of the Greater Nottingham area. This encompasses a population of over 621,000 (500,746 adults aged ≥16 years) at the last census (2001), and includes Nottingham City, the Boroughs of Broxtowe, Gedling and Rushcliffe, and the Hucknall part of Ashfield District (www.nottinghamcity.gov.uk). The majority of this population are classified in the 2001 census as "White British" at just over 567,000 people (91.3%). Data are not available on migration rates for the greater Nottingham area, but for Nottingham City the migration rates of people from outside the area were less than 10% of total population. Nottingham therefore represents a stable population in a medium-sized UK city, and is ideal for such a population-based study.

The health needs of this area are served by only two large hospitals (Queen's Medical Centre (QMC) and Nottingham City Hospital (NCH)) of around 1000 beds each, comprising one teaching hospital trust (Nottingham University Hospitals NHS Trust). All patients requiring hospitalisation are admitted to one of these hospitals. Admissions arrive either via referral from a primary care practitioner or from the emergency department (ED). Admissions to the medical directorate come to one of three acute medical units on the two sites.

Study design

Between September 2008 and September 2010, consecutive adult patients (aged ≥16 years) admitted with CAP were prospectively identified on a daily basis from the acute medical areas of both trusts. Potential participants were identified by liasing with the relevant resident junior doctors. For practical purposes only the respiratory, acute medical and critical care wards in both hospitals were visited to recruit patients, and weekends and bank holidays were excluded. Only one visit to each ward was made daily. This inevitably meant that a number of potential participants were missed. However, there should be no systematic reason why missed patients should differ clinically or microbiologically from those included in the study. Fifty-nine percent of

participants were recruited by the author, with the remainder recruited by the research nurse Sonia Greenwood.

Patients were included if they:

1. Had at least one acute symptom in keeping with a lower respiratory tract infection (breathlessness, cough, sputum or fever);
2. Were aged ≥16 years;
3. Had new infiltrates on a chest radiograph;
4. Were treated by the admitting team for CAP.

Patients were excluded if:

1. They had been admitted to hospital in the preceding 10 days;
2. Had tuberculosis;
3. Had post-obstructive pneumonia due to lung cancer.

Patients were not excluded if they were immunosuppressed or if the admission were an expected terminal event. Participants were identified by study investigators on a daily basis from the acute admitting medical wards and enrolled following informed consent. All patients were managed in a similar manner according to hospital CAP guidelines at the discretion of the attending clinician. Full ethical approval for the study was granted by the Nottingham Regional Ethics Committee. Informed consent was obtained from each patient, and if the patient were unable to consent due to a lack of capacity, informed assent was sought from a relative. If appropriate, participants were seen in an outpatient clinic six to eight weeks following discharge to assess clinical and radiological disease resolution. Ethical approval; was also gained for review of the medical notes (but *not* acquisition or retention of clinical samples) of patients in whom consent was not available after completion of the admission episode (for example, due to early discharge or death).

Clinical data and study samples

Following informed consent, a standard study proforma was used to record data on the patient and admission episode. The included fields were:

- Demographics data, including age, sex, and if admitted from a nursing or residential home;
- A record of symptoms as measured by the CAP score (appendix 2);
- Admission and baseline functional status was estimated using the World Health Organisation performance status scoring system.[369] Admission performance status was determined by the study investigators, whereas baseline performance status was estimated from patient descriptions of their functional status prior to the onset of disease;
- Admission blood tests, including full blood count, urea and electrolytes, and C-reactive protein (CRP);
- Self reported rates of influenza vaccination in the 12 months preceding admission, and PPV in the 10 years preceding admission;
- Measures of disease severity including CURB-65 and PSI;
- Co-morbidity;
- Details of radiographic changes, with timings;
- Details of antibiotic treatment, with timings;
- Physiological observations on admission, and for the succeeding three days if available;
- Complications of CAP, including effusion and empyema;
- Outcomes, such as 30-day mortality, admission to critical care (CC) and need for invasive respiratory or vasopressor support (IVRS), 30-day re-admission, and length of hospital stay (LOS);
- Results of microbiological investigations, including those requested by the admitting team.

Microbiological methods

To identify those patients who had pneumococcal disease, a urine specimen was obtained following informed consent from each patient. This sample was thereafter used in two microbiological tests; the immunochromatographic assay Binax NOW® and the Bio-Plex assay. The Binax NOW® assay is a microbiological test in current routine clinical use (see chapter 3), and was performed on receipt of the study samples in the Nottingham University Hospitals Microbiology department, a UK Health Protection Agency (HPA) regional laboratory, by the microbiology technicians. The urine samples were subsequently stored in a dedicated study freezer at -20°C, and transported by the author to the Respiratory and Systemic Infection Laboratory (RSIL) at the Centre for Infections (CfI) at the HPA Colindale, London, where they were tested by the resident biomedical scientists in batches using the pneumococcal serotype-specific Bio-Plex assay, as described below.

Binax NOW®

During a pneumococcal infection, the polysaccharide coat is shed and excreted in the urine, and this antigen persists in the host for at least seven days.[370] The efficacy of this assay has been described in chapter 3. The test kit consists of a nitrocellulose membrane test strip with two lines of adsorbed antibody, one rabbit anti-pneumococcal C-polysaccharide antibody and one control antibody. Both antibodies are conjugated to a substance that colours blue when the antibody is bound. A swab is inserted into the device after it is dipped in the test sample, and a citrate/phosphate buffer added. If pneumococcal capsular polysaccharide is present, both test and control lines will turn blue within 15 minutes. Binax NOW® has a substantially better sensitivity for detecting pneumococcal disease than standard cultures, but a further assay is required to determine the serotype.

Bio-Plex

ELISA assays have been developed before for detection of capsular antigen in urine, but whilst high sensitivities (>80%) and specificities (>98%) were achieved, the

process was laborious and had high volume and reagent requirements.[371] In order to make the assay more viable for processing of large numbers of samples simultaneously, a multiplex ELISA is required. The Bio-Plex assay has recently been developed at the Respiratory and Systemic Infection Laboratory (RSIL) at the Health Protection Agency (HPA) in Colindale, London,[372] and is a modified sandwich ELISA assay. Polystyrene microspheres, 5.5µm in diameter (Luminex xMAP beads; Luminex Corp., Texas, USA), are labelled with dyes of different colours between red and infrared, allowing differentiation into 100 different spectral types. These are then conjugated to one of 14 different pneumococcal monoclonal serotype-specific antibodies (1, 3, 4, 5, 6A, 6B, 7F/A, 8, 9V, 14, 18, 19A, 19F, or 23F). The conjugated microspheres are suspended with the clinical sample and incubated overnight, binding any serotype-specific capsular antigen present. Rabbit polyclonal pneumococcal antibody is then added and used as a detection antibody, attached to the fluorochrome R-phycoerythrin. The sample is then passed through the Bio-Plex multi-analyte suspension array instrument (Bio-Rad, Hemel Hempstead, UK) which is calibrated using the Bio-Plex calibration kit (Bio-Rad). The microspheres are passed through two lasers; one classifies each microsphere by the inherent dye colour, and the other excites the fluorochromes bound to the sandwich microsphere-antigen-antibody complex, allowing quantification of the amount of antigen present. The full standard operating procedure is included in appendix 1.

The advantage of using this procedure is that it allows the differentiation of multiple serotypes within one clinical sample, and as such a multitude of samples can be assayed for a variety of serotypes simultaneously, significantly reducing the time taken to detect serotype. The sensitivity and specificity of the assay have recently been reported as 79.3% and 99.3% respectively using a contemporaneous positive pneumococcal blood culture as the gold standard.[372]

There are several disadvantages to this technique. Compared with Binax NOW® the Bio-Plex assay is time consuming and complex. This makes it of more use as a

research tool rather than in real-time as part of an admission episode. Secondly, the range of detectable serotypes is limited, particularly given the potential emergence of some previously rare serotypes following the introduction of PCV-7 and PCV-13.

Other microbiological techniques

The results from other samples sent as part of routine clinical care using conventional microbiological methods were also recorded from the hospital computerised patient records. Data collected in this way included the results from sputum and blood cultures, and *Legionella pneumophila* urinary antigen results. These results were only available if sent by the clinical team under whose care the participant fell. Pneumococcal serotype was also determined in pneumococcal bacteraemic patients by means of slide agglutination with the latex pool sera from Staten Serum Institute (SSI) and the standard group or factor sera at the RSIL at HPA Colindale, London.

Summary

This chapter has described the rationale and methodological process for the majority of studies contained within this thesis. Successive chapters will describe the results of data gathered over the two year period of the study.

Chapter 5: Distribution and epidemiology of pneumococcal serotypes

“The capsule contains a specific soluble substance…of high molecular weight and polysaccharide nature, distinctive both in quantity and in molecular structure…”

“Diseases of the Chest”, Dr Robert Coope (1944)

Introduction

As described in chapter 2, the majority of studies describing the serotype distribution for pneumococcal CAP have used data derived from blood cultures.[102, 110, 121] However, blood cultures are positive in around only 5% of adults with CAP,[223, 242, 243] and it is not known if IPD data are representative of non-invasive disease. Non-cultural methods for determining pneumococcal serotype have a substantially higher sensitivity,[371-374] but to date there have been no large studies describing the incidence of pneumococcal serotypes in non-invasive CAP.

The seven-valent pneumococcal conjugate vaccine (PCV-7) was added to the UK immunisation schedule in September 2006. Following its introduction in the USA, decreases in PCV-7 vaccine-type (VT) serotypes were seen in invasive pneumococcal disease (IPD) in children,[199, 375, 376] and adults,[194-196] and in nasopharyngeal carriage in vaccinated children,[186] and non-vaccinated household contacts.[58] It is not known whether large scale vaccination of children is changing the epidemiology of pneumococcal CAP in adults in the UK, and therefore changing the spectrum of adult pneumococcal disease. The current study aims to a) describe the distribution of pneumococcal serotypes in invasive and non-invasive pneumococcal CAP, b) describe the serotype-associated epidemiology, with particular focus on seasonality and age, and c) to investigate the attack rates for serotypes of high and low invasiveness in different age groups.

Methods

Patient recruitment

This study refers to participants recruited as described in chapter 4.

Definitions

Patients were defined as having pneumococcal CAP if any microbiological test was positive for *S. pneumoniae*, including blood culture, sputum culture, Binax NOW®, or Bio-Plex serotype-specific antigen detection. Patients with pneumococcal CAP where

no serotype was detected after testing with the Bio-Plex assay (i.e. *S. pneumoniae* detected by Binax NOW® or sputum culture, but no serotype determined by Bio-Plex or blood culture) were described as having "untyped" pneumococcal disease. Serotypes included in PCV-7 (4, 6B, 9V, 14, 18C, 19F, 23F) are hereafter referred to as "vaccine-type" (VT), and serotypes not contained within PCV-7 as "non vaccine-type" (NVT). All VT serotypes are detectable by the Bio-Plex assay. Invasive serotypes were defined as 1, 5, 7F and 8 according to previous publications,[103, 115, 121] with the other detected serotypes defined as less invasive serotypes.

Annual incidence rates for all-cause and pneumococcal CAP was calculated using the latest census figures (from 2001) for the greater Nottingham area, with an adult population of 500,746 (www.nottinghamcity.gov.uk/index.aspx?articleid=2401). Age group thresholds were the same as those used in the Nottingham census data:

- 16-24 years;
- 25-44 years;
- 45-59 years;
- 60-74 years;
- 75-84 years;
- ≥85 years;

Age groups one and two were combined for the purposes of serotype analysis due to the low numbers of participants in both groups. Seasons were defined according to meteorological convention as follows:

- Autumn: September to November;
- Winter: December to February;
- Spring: March to May;
- Summer: June to September.

Statistical considerations

Statistical calculations were made using SPSS v16.0 (©SPSS Inc., 1989-2007). Categorical data were compared using Pearson's χ^2, which was also used for univariate analysis and generation of odds ratios (OR). A p-value of less than 0.05 was taken as statistically significant. A binary logistic regression analysis was used to investigate the association between pneumococcal aetiology and season, with adjustment made for pneumonia severity as defined by the PSI (see chapter 3).

Results

Of 1099 patients identified with CAP during the study period, 956 consented to be included in the study. Thirty-six patients were unable to provide a urine sample (and had no other test positive for pneumococcus), leaving 920 for analysis. Demographic data for the cohort are presented in table 5.1. The median age of the cohort was 71.7 years (interquartile range (IQR) 57.8-80.8), and 64.4% were aged ≥65 years. The 30-day mortality for the cohort was 10% (9.5% for patients with pneumococcal CAP), and 82 patients (8.9%) required IRVS (table 5.1). Median LOS was 7 days (interquartile range (IQR) 4-12 days).

Patient characteristics	Whole cohort (n=920)
Demographics	
Age, median; years (IQR)	71.7 (57.8-80.8)
Male (%)	546 (59.3)
Residential or nursing care home resident (%)	51 (5.5)
WHO Performance Status ≥2 (%)	138 (15.0)
COPD (%)	244 (26.5)
Ischaemic heart disease (%)	145 (15.8)
Diabetes mellitus (%)	130 (14.1)
Cerebrovascular disease (%)	103 (11.2)
Asthma (%)	102 (11.1)
Congestive cardiac failure (%)	74 (8.0)
Active malignancy (%)	67 (7.3)
Dementia (%)	32 (3.5)
Mean Charlson co-morbidity index (95% CI)	1.48 (1.37-1.59)
Influenza vaccination in preceding 12 months (%)	558/855 (65.3)
PPV in preceding 10 years (%)	383/824 (46.5)
Severity	
PSI Class I-III (%)	395 (42.9)
PSI Class IV (%)	336 (36.5)
PSI Class V (%)	189 (20.5)
Outcome	
30-day mortality (%)	92 (10.0)
LOS	7 (4-12)
IRVS (%)	82 (8.9)

IQR: interquartile range; WHO: World Health Organisation; COPD: chronic obstructive pulmonary disease; CI: confidence interval; PPV: pneumococcal polysaccharide vaccine; PSI: pneumonia severity index; LOS: length of hospital stay; IRVS: invasive respiratory or vasopressor support.

Table 5.1. Demographic data of the study cohort.

Age distribution and incidence

Annual CAP incidence figures were calculated including the patients with CAP who were unable to consent or provide a urine sample (n=1099). The derived annual incidence of CAP within this population was 109.8 per 100,000 over the two years studied; 124.2 per 100,000 for the first year studied, and 95.3 per 100,000 for the second year. The annual incidence of CAP increased with age from 15.8 per 100,000 for ages 16-24 to 985.9 per 100,000 for those aged more than 85 years (table 5.2).

Age group	Population	CAP (n)	Year 1	Annual incidence year 1 (per 100,000)	Year 2	Annual incidence year 2 (per 100,000)
16-24	82,471	26	17	20.6	9	10.9
25-44	181,187	115	58	32.0	57	31.5
45-59	111,837	140	71	125.2	69	61.7
60-74	79,737	295	162	203.2	133	166.8
75-84	34,204	300	173	505.8	127	371.3
85+	11,310	223	141	1246.7	82	725.0
All ages	500,746	1099	622	124.2	477	95.3

"Population" refers to the number of people in the greater Nottingham area in the 2001 census. "Year 1" represents 10th September 2008 to 9th September 2009; year 2 represents 10th September 2009 to 10th September 2010. CAP: community-acquired pneumonia.

Table 5.2. The incidence of community-acquired pneumonia by age group.

Pneumococcal CAP

Of the 920 patients included in the study, pneumococcal CAP was diagnosed in 366 patients (39.8%); 40 cultured *S. pneumoniae* from blood and 18 from sputum or broncho-alveolar lavage, and 196 (21.3%) patients had a positive Binax NOW® result. For 144 patients in whom Binax NOW® testing was negative, a serotype was determined by Bio-Plex. Other pathogens identified from routine microbiological testing included *Legionella pneumophila* serogroup 1 (based on urinary antigen detection with a Binax NOW® assay) in 17/463 (3.7%) patients tested, *Pseudomonas aeruginosa*, from sputum culture in 24/367 (6.5%) patients, and *Haemophilus influenzae* from sputum culture in 24/367 (6.5%) patients. In four cases *Haemophilus influenzae* was cultured in sputum as a co-pathogen with *S. pneumoniae*.

The proportion of patients with confirmed pneumococcal CAP compared with CAP of unknown aetiology decreased with increasing age group, but only reached statistical significance when compared with youngest age group (aged 16-44) for the age group 60-74 (OR 0.6, 95% CI 0.4-0.9; p=0.027) (table 5.3). Pneumococcal aetiology became more prevalent again in the very elderly (age 85 or more). Self-reported influenza and adult pneumococcal vaccination (PPV) data were available for 855 (92.9%) and 824 (89.6%) patients respectively. Vaccination rates were highest in older age groups (table 5.4). Prior vaccination with PPV was not associated with infection with lower rates of pneumococcal infection (OR 1.0, 95% CI 0.7-1.3; p=0.803), but was associated with lower levels of bacteraemia on univariate analysis (OR 0.4, 95% CI 0.2-0.8, p=0.009). However, after adjustment was made for age group this difference was no longer statistically significant (OR 0.6, 95% CI 0.2-1.3, p=0.188).

Age group	Pneumococcal CAP (%)	OR of pneumococcal CAP vs. all CAP (95%CI)	P value	VT serotypes	OR of VT vs. NVT CAP (95%CI)	P value
16-44 (n=136)	64 (47.1)	1	-	7	1	-
45-59 (n=129)	51 (39.5)	0.7 (0.5-1.2)	0.217	10	1.9 (0.6-5.5)	0.255
60-74 (n=272)	97 (35.7)	0.6 (0.4-0.9)	**0.027**	21	2.8 (1.1-7.3)	**0.037**
75-84 (n=242)	92 (38.0)	0.7 (0.5-1.1)	0.087	18	2.5 (0.9-6.7)	0.066
85+ (n=141)	62 (44.0)	0.9 (0.6-1.4)	0.606	16	3.8 (1.4-10.6)	**0.011**
All ages (n=920)	366 (39.8)	-	-	72	-	

CAP: community-acquired pneumonia; OR: odds ratio; VT: serotypes included within the 7-valent childhood pneumococcal vaccine (4, 6B, 9V, 14, 18C, 19F, 23F); NVT: serotypes not included within the 7-valent childhood pneumococcal vaccine. P values refer to odds ratios in older age groups when compared with age group 16-44.

Table 5.3. The proportion of pneumococcal disease in the cohort, by age group.

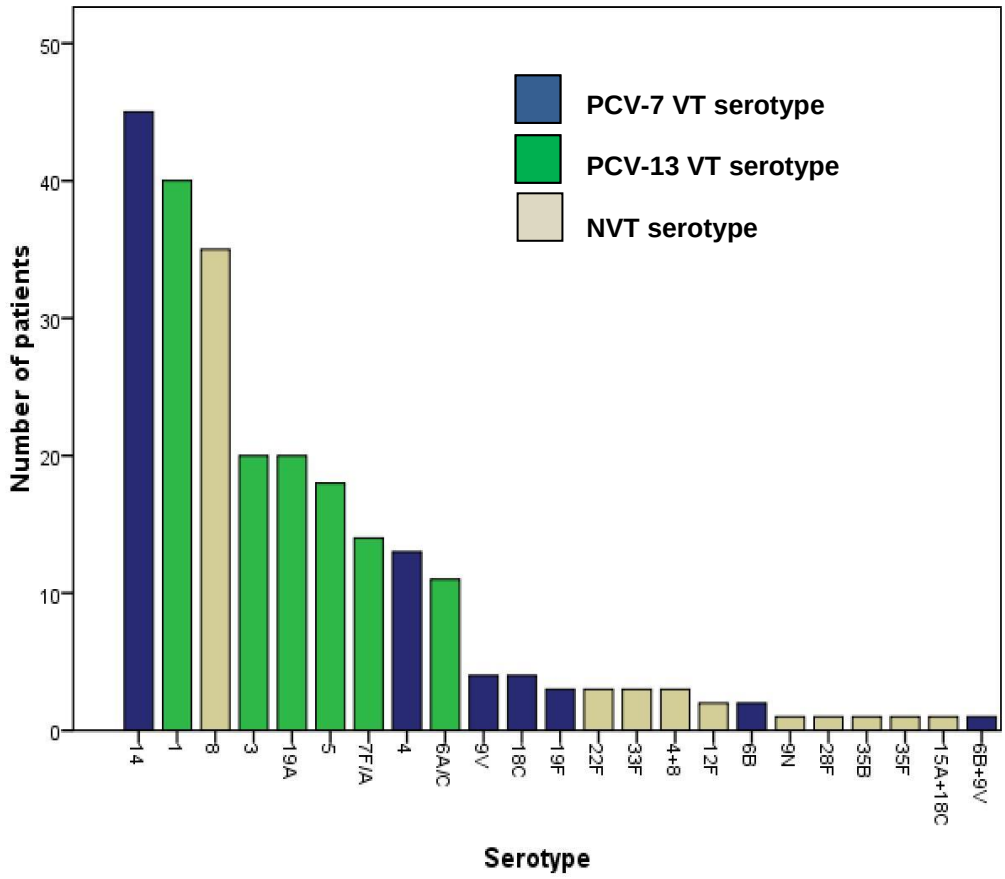
	PPV (%) (n=824)	Influenza (%) (n=855)
16-44	8 (6.1)	25 (18.8)
45-59	36 (28.3)	63 (49.6)
60-74	135 (54.2)	192 (75.0)
75-84	133 (66.5)	172 (82.3)
85+	71 (60.7)	106 (81.5)
All ages	383 (46.5)	558 (65.3)

Vaccination data are self reported. PPV: pneumococcal polysaccharide vaccine.

Table 5.4. Proportion of patients receiving pneumococcal and influenza vaccination.

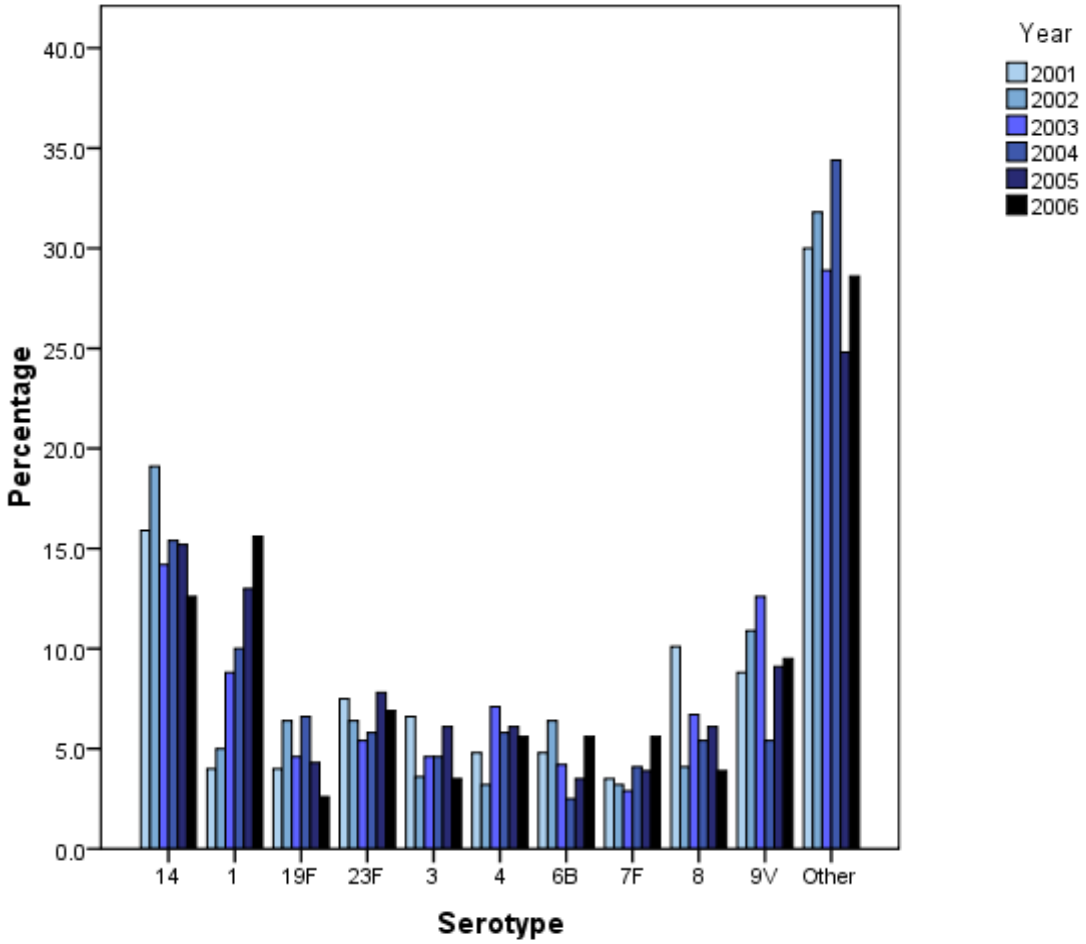
Serotype distribution

The distribution of pneumococcal serotypes within the cohort is shown in figure 5.1. Of 366 patients with pneumococcal CAP, a serotype was determined in 242 patients. The serotype with the highest prevalence was 14 (n=45), followed by 1 (n=40), 8 (n=35), 3 (n=20), and 19A (n=20). For comparison, the distribution of serotypes in IPD in the UK prior to the introduction of PCV-7 is shown in figure 5.2. Five patients had two serotypes identified; three with serotypes 4 and 8, one with serotypes 6B and 9V, and one with serotypes 15A and 18C. Serotypes contained within PCV-7 were found in 72 patients. The proportion of disease due to serotypes contained within PCV-7 increased with age (7/45 (15.6%) for patients aged 16-44; 21/62 (33.9%) for patients aged 60-74; 16/39 (41.0%) for patients more than 85 years; $p<0.05$ for both) (table 5.3).



VT: serotypes included within the childhood pneumococcal vaccine; NVT: serotypes not included within the childhood pneumococcal vaccine; PCV-7: 7-valent pneumococcal conjugate vaccine; PCV-13: 13-valent pneumococcal conjugate vaccine.

Figure 5.1: Serotype distribution of the study cohort.



Adapted from Farrell et al., 2008.[102]

Figure 5.2: Serotype distribution of bacteraemic invasive pneumococcal disease in a large UK cohort prior to the introduction of the pneumococcal conjugate vaccine.

Serotype-specific attack rates

The annual age-specific incidence for both highly invasive and less invasive serotypes increased with age (table 5.5). This effect was more marked in the older age groups, where the annual incidence of less invasive serotypes was far higher (annual incidence in patients aged ≥85 years: invasive serotypes 30.9 per 100,000; less invasive serotypes 141.5 per 100,000). Both increasing age group and co-morbidity group were significant predictors of acquisition of a less invasive serotype (OR per age group 1.5, 95% CI 1.2-1.9, $p<0.001$; OR per co-morbidity group 1.4, 95% CI 1.0-2.0, $p=0.036$).

	Highly invasive serotypes, n (per 100,000 per year)	Less invasive serotypes, n (per 100,000 per year)
16-44	28 (5.3)	17 (3.2)
45-59	24 (10.7)	15 (6.7)
60-74	27 (16.9)	35 (21.9)
75-84	21 (30.7)	36 (52.6)
85+	7 (30.9)	32 (141.5)

Table 5.5. Serotype-specific attack rates.

Seasonality

Admissions to hospital with CAP were more frequent during the winter months, with most admissions between October and January (figures 5.3 and 5.4, table 5.5). Pneumococcal disease was more prevalent as a proportion of CAP cases in the winter (137/304, 45.1%) when compared with autumn (89/243; 36.6%), spring (82/221, 37.1%) and summer (58/152; 38.2%) (p=0.047) (table 5.5). Using admissions in January as a comparator, patients admitted in September were significantly less likely to have a pneumococcal aetiology (44.1% versus 25.0%; OR 0.39, 95% CI 0.19-0.79; p=0.009). These observations retained statistical significance at the 5% level after adjustment was made for pneumonia severity using PSI class.

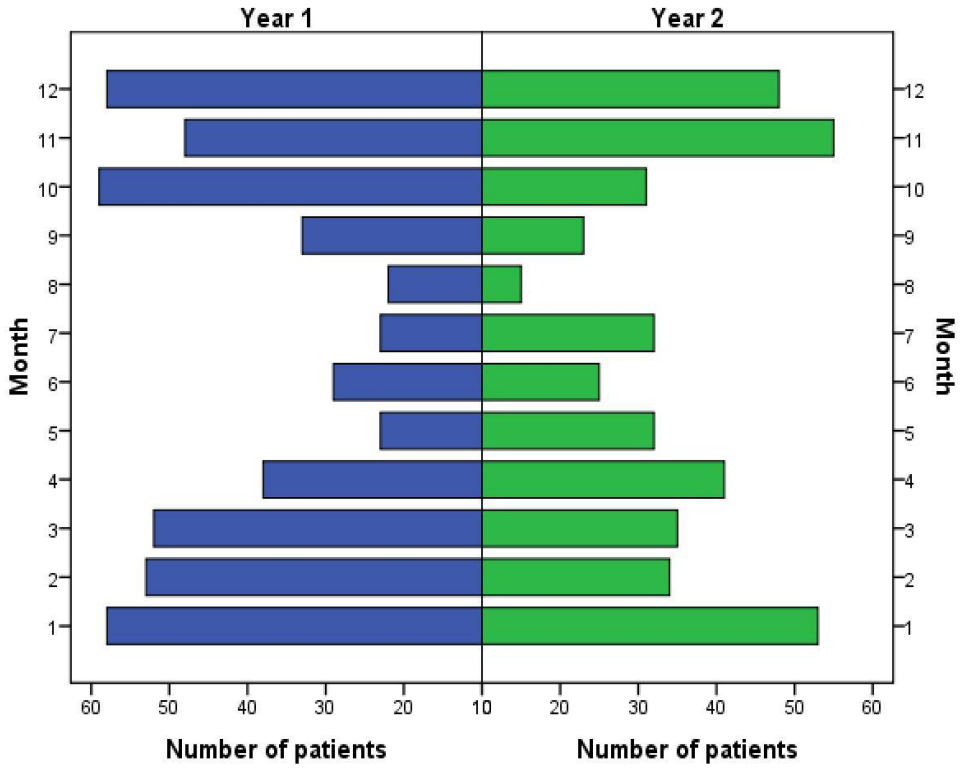


Figure 5.3. Distribution of proportion CAP admissions by month of year.

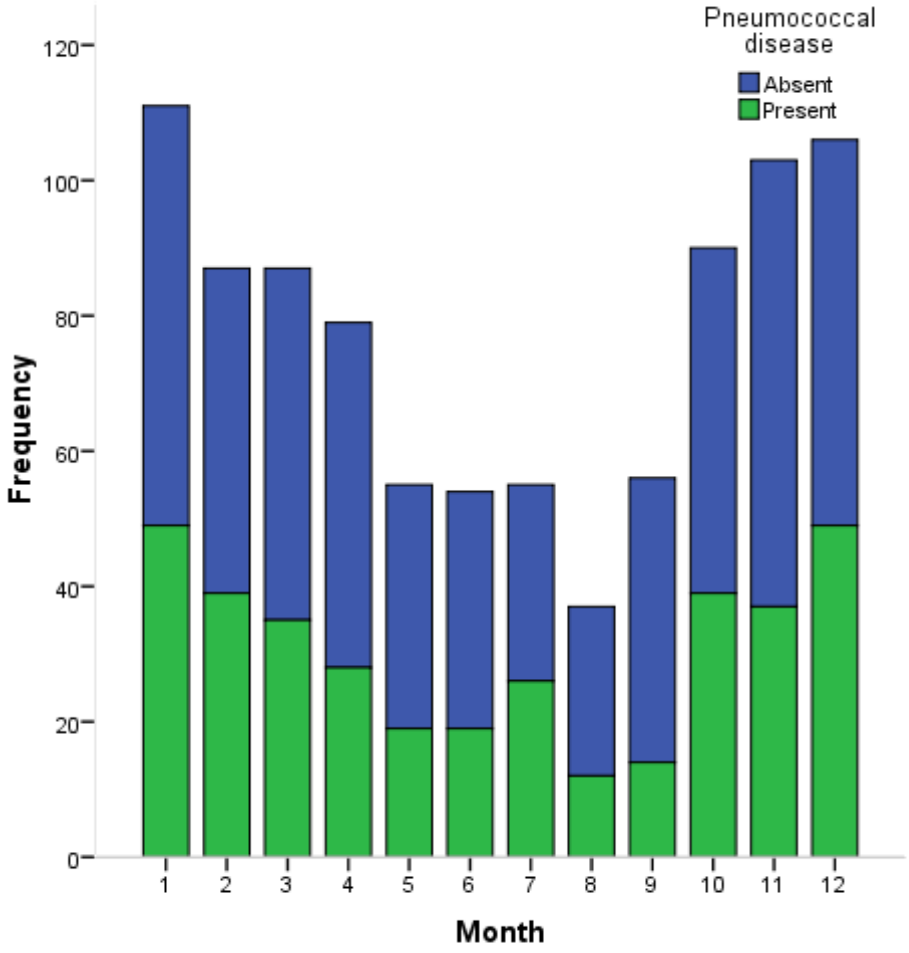


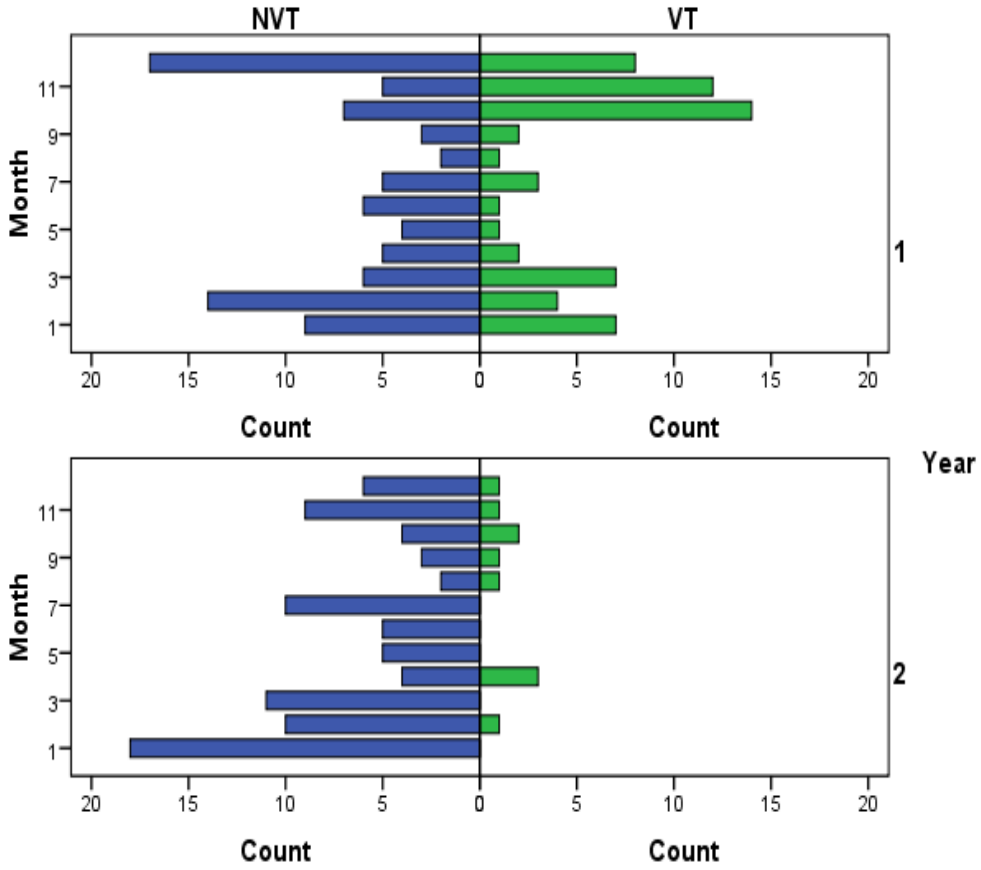
Figure 5.4. Admissions with pneumococcal CAP by month of the year.

	Population incidence (per 100,000 per month)	Pneumococcal CAP (%)
January (n=111)	11.1	49 (44.1)
February (n=87)	8.7	39 (44.8)
March (n=87)	8.7	35 (40.2)
April (n=79)	7.9	28 (35.4)
May (n=55)	5.5	19 (34.5)
June (n=54)	5.4	19 (35.2)
July (n=55)	5.5	26 (47.3)
August (n=37)	3.7	12 (32.4)
September (n=56)	5.6	14 (25.0)
October (n=90)	9.0	39 (43.3)
November (n=103)	10.3	37 (35.9)
December (n=106)	10.6	49 (46.2)
Spring (n=221)	7.4	82 (37.1)
Summer (n=152)	5.1	58 (38.2)
Autumn (n=243)	8.1	89 (36.6)
Winter (n=304)	10.1	137 (45.1)*

*:p<0.05 when compared with patients admitted in autumn.

Table 5.6. Monthly incidence of all-cause CAP admissions.

Of the 242 patients in whom a serotype was determined, 145 were in year one and 97 in year two. Absolute numbers of NVT serotypes remained approximately the same between years one and two (83 and 87 respectively), but the numbers of VT serotypes fell from 62 to 10 over the same period (figure 5.5).



VT: serotypes included within the 7-valent childhood pneumococcal vaccine (4, 6B, 9V, 14, 18C, 19F, 23F); NVT: serotypes not included within the 7-valent childhood pneumococcal vaccine.

Figure 5.5. The distribution of serotypes found in years one and two of the study.

Discussion

This study is the first to describe the serotype distribution in a cohort of adult pneumococcal CAP incorporating both invasive and non-invasive disease. The principal findings are as follows:

- The population-specific incidence of CAP increases with age, but the likelihood of pneumococcal aetiology falls. However, older patients are more likely to have infection with a VT serotype.
- The commonest serotypes present within this cohort in descending order of prevalence were 14, 1, 8, 3, and 19A. These are similar to the findings of previous IPD cohorts in the UK, with the exception that VT serotypes (in particular 23F, 19F, 6B and 9V) are less frequently found, whereas NVT serotypes (particularly serotypes 8 and 19A) are more prevalent within this non-invasive cohort.
- Both pneumococcal and all-cause CAP are more common in winter than other seasons.
- VT serotypes were substantially less prevalent in the second year of the study compared with the first, whilst the absolute number of NVT serotypes remained approximately the same.

The age-specific incidences found in this study for pneumococcal CAP are substantially higher than those suggested elsewhere in CAP database studies.[33] This may reflect the improved sensitivity of the Binax NOW® and Bio-Plex assays for pneumococcal disease over standard culture-based methods. The proportion of disease due to serotypes contained within PCV-7 was higher in the older age groups. This parallels findings in IPD cohorts, where serotypes commonly seen in childhood disease become more prevalent again in the elderly.[124] The reasons underlying this are not well understood, but potentially this finding could reflect deterioration in immune system efficacy with advancing age. Additionally, older people may have less exposure in general to younger children. As discussed in chapter 2, children are

thought to be the principal reservoir of pneumococcal carriage and therefore transmission. Following the introduction of PCV-7 and the reduction in VT serotype carriage amongst vaccinated children, NVT serotypes may be preferentially transmitted to those adults who have most contact with vaccinated children. This possibility will be explored in more detail in chapter 7.

The distribution of serotypes in this study is similar to previously published UK data.[102] This suggests that for the purposes of surveillance, IPD cohorts provide a reasonable estimate of the serotype distribution of both invasive and non-invasive pneumococcal CAP within the population. Serotypes 8 and 19A have a higher prevalence within the current cohort than would be expected from IPD data. There are two possible reasons for this finding. These serotypes may be over-represented in our cohort due to difficulties in culturing them using standard techniques, and hence the prevalence is falsely underestimated in previous IPD studies. Alternatively, these serotypes may be preferentially emerging due to vaccine-induced population pressures on child nasopharyngeal carriage, and over the coming years may be much more prevalent as a cause of adult disease. This is particularly relevant for serotype 8, which is not included in either PCV-7 or the newer PCV-13, introduced to childhood vaccination schedules in April 2010.

The serotypes which are more prevalent in the pre-vaccine era UK IPD cohorts than in the current study are 23F, 19F, 6B and 9V, all of which are VT serotypes. There was also a striking difference in the proportions of NVT and VT serotypes between the two years studied, with a substantial decrease in the proportion of VT serotypes in the second year. It is again tempting to ascribe this difference to the increasing impact of PCV-7 on child VT carriage rates over the period of the study, progressively reducing transmission of VT serotypes to adults. A concomitant increase in NVT serotypes in year 2 was not seen in this study. However, substantial annual variation in serotypes in IPD has been documented in the UK in previous years,[102] and therefore more years of data would be required to demonstrate such an effect with adequate statistical

robustness. The H1N1 swine-origin influenza pandemic also occurred in the second winter of the study. H1N1 influenza almost completely replaced standard seasonal influenza types during this period, and in the majority of cases resulted in a milder clinical phenotype.[377-380] Therefore this may also have influenced the spectrum and number of pneumococcal infections given the association between influenza and pneumococcal disease.

Serotype-specific attack rates increased with increasing age group, but much less so for the invasive serotypes than other serotypes. Invasive serotypes are thought to act as "primary pathogens", causing disease instead of nasopharyngeal colonisation,[108] perhaps because of the relatively thin capsule that these serotypes possess.[121] By extension this would imply that the attack rates for invasive serotypes should be broadly similar across all age groups, as potential to cause disease is more affected by pathogen than host factors. In contrast, less invasive serotypes acting as opportunistic pathogens should preferentially affect older patients with higher levels of co-morbidity and frailty. This hypothesis is supported by the findings of this study.

The incidence of pneumococcal CAP was highest in the winter months, a finding replicated elsewhere.[381] There are a number of possible explanations for this. Several publications have shown an association between influenza or other respiratory virus infection (such as respiratory syncytial virus) and IPD, with a lag time of between one and three weeks after viral infection.[382-385] Suggested mechanisms for this observation have been epithelial damage via removal of sialic acid residues by the neuraminidase component of influenza, promoting pneumococcal adherence to infected lungs,[386] and immune modulation, in particular via excessive IL-10 (an anti-inflammatory cytokine) production.[387] A number of studies have examined the role of weather and temperature in the incidence of pneumococcal CAP, and conclusive correlations are yet to be found. However, one recent study did find that low levels of ultraviolet light levels correlated with an increase in the incidence of IPD.[388]

PPV vaccination was not protective for pneumococcal CAP in this study. There was an association on univariate analysis between bacteraemic pneumococcal pneumonia and lack of prior PPV vaccination (p=0.009), but when adjustment was made for age and co-morbidity statistical significance was not reached (p=0.17). These findings reflect the lack of convincing data for the efficacy of PPV in preventing pneumococcal CAP,[158] and support the continued development and use of the newer conjugate vaccines for use in adults.

Study limitations

A significant proportion (124/366; 33%) of pneumococcal disease in this study was labelled as untyped. This may reflect either the presence of serotypes beyond the fourteen detectable by the Bio-Plex assay, or the limited sensitivity of the Bio-Plex assay itself. If the former, then there may be significant NVT serotype(s) that are not being described by this study. The sensitivity of Bio-Plex has been estimated at 79%,[372] and therefore a proportion of potentially detectable serotypes will inevitably have been missed. The untyped group were intermediate between VT and NVT serotype groups with regards to 30-day mortality (untyped: 10·8%; VT: 16·7%; NVT: 5·9%) and co-morbidity (mean Charlson co-morbidity index, untyped 1·68; VT 1·97; NVT 1·36). One interpretation of this observation is that the untyped group represents a combination of serotypes from both VT and NVT serotype groups. Alternatively, the serotypes represented in the untyped group may be associated with CAP with different clinical characteristics. Due to the very high specificity of the Bio-Plex assay (>99%), it is unlikely that a particular serotype has been mis-assigned.

This study was carried out at two large hospitals covering a relatively stable catchment population of approximately 700,000 in Nottingham. As there are no other hospitals in the area, all patients with CAP requiring hospitalisation are admitted to either of the two study hospitals. Therefore, selection bias due to differences in hospital admission practices is unlikely. However, as this study included only hospitalised cases these findings may not apply to patients with CAP in the

community with less severe disease. Larger, multi-centre studies in more diverse populations of patients are therefore required.

Conclusions

The commonest serotypes implicated in non-invasive pneumococcal pneumonia are 14, 1, 8, 3 and 19A. The epidemiology of these serotypes varies considerably by age and season, with fewer PCV-7 vaccine-type serotypes seen in the second year of the study. Invasive serotypes have similar attack rates across age groups whereas less invasive serotypes predominantly cause disease in older patients with more co-morbidity.

Chapter 6: Association of pneumococcal serotype with clinical phenotypes

"…type III pneumococcus is perhaps the most fatal of all types, not because these pneumococci are in themselves the most virulent, but because they especially attack old people."

"Diseases of the Chest", Dr Robert Coope (1944)

Introduction

As described in chapter 2, the distribution of pneumococcal serotypes in adult CAP may be changing following the introduction of PCV-7. The serotype distribution for the current cohort is described in the previous chapter, but the relevance of this is yet to be elucidated. The infecting serotype may have implications for the clinical spectrum of pneumococcal disease. In cohorts of adults with invasive pneumococcal disease (IPD), particular serotypes have been associated with meningitis,[103] and development of septic shock.[130] Furthermore, certain serotypes have been linked to increased 30-day mortality and higher severity disease.[105, 108, 110, 121]

The aim of this study was to describe the clinical features and outcomes for adults hospitalised with both invasive and non-invasive pneumococcal CAP according to pneumococcal serotype.

Methods

Participants

Participants were recruited as per the methods described in chapter 4.

Outcome measures

The main clinical outcome measure correlated with pneumococcal serotype was death within 30 days of admission. Secondary outcome measures were the need for invasive or non-invasive ventilation or refractory shock requiring vasopressor support (IVRS), and length of hospital stay (LOS). Clinical features that were recorded as secondary outcomes included presence of hypotension on admission (defined as systolic blood pressure <90mmHg), chest radiographic appearances, admission C-reactive protein (CRP), and co-morbidity estimated using the Charlson co-morbidity index.[389] Demographic data (including age and sex), disease severity as measured by the Pneumonia Severity Index (PSI), co-morbidity, baseline WHO performance status, and self reported rates of influenza and PPV vaccination were also recorded.

Statistical analysis

Statistical calculations were made using SPSS v16.0 (©SPSS Inc., 1989-2007). Categorical data were compared using Pearson's χ^2, which was also used for calculating odds ratios (OR) and 95% confidence intervals (CI). Continuous data that were non-normally distributed were compared using Mann-Whitney U test.

The associations between serotypes and outcomes were assessed using a logistic regression model, with adjustment made for age (with groups representing ages 16-49, 50-64, 65-74, 75-84 and 85+ years according to epidemiological convention) and co-morbidity (as measured by the Charlson co-morbidity index,[389] grouped into no (score 0), mild (1-2), moderate (3-4) or severe (5+) co-morbidity). The "adjusted odds ratios" quoted in the text are following adjustment for age and co-morbidity unless otherwise stated. Where appropriate, adjustment was alternatively made using the PSI severity group. In comparisons between individual serotypes, the untyped group was used as the comparator.

As mentioned in the previous chapter, five patients had two serotypes identified; three with serotypes 4 and 8, one with serotypes 6B and 9V, and one with serotypes 15A and 18C. These patients were not included in any analyses involving comparisons between individual serotypes. As serotypes 6B and 9V are both included within PCV-7, this patient was included as part of the VT serotype group.

Results

Vaccine-type serotypes

VT Serotypes were identified in 72 (29·8%) of 242 patients in whom a serotype was determined, excluding the four patients where both a VT and NVT serotype was found. Pneumonia with a VT serotype was associated with older age (median 73·5 years vs. 65·9 years; p=0·003) and higher levels of co-morbidity (mean Charlson co-morbidity index 1·97 vs. 1·32; p=0·036) compared to NVT serotype pneumonia (table

6.1). Pneumonia with a VT compared with NVT serotype was associated with higher 30-day mortality after adjustment for disease severity (OR 3·0, 95% CI 1·2-7·5; p=0·016) or age and co-morbidity (OR 2·8, 95% CI 1·1-7·2, p=0·035) (table 6.1). There were no differences in LOS or IVRS for CAP with VT serotypes compared with NVT serotypes. NVT disease was associated with a higher proportion of patients presenting with hypotension (systolic blood pressure <90mmHg) (17·4% vs. 5·6%; adjusted OR 4·1, 95% CI 1·3-12·8, p=0·017) and pleural effusions (34·1% vs.19·4%; adjusted OR 2·0, 95% CI 1·0-3·9, p=0·050) (table 6.2).

Patient characteristics	Whole cohort (n=920)	Untyped (n=120)	VT (n=72)	NVT (n=170)	P value*
Demographics					
Age, median; years (IQR)	71.7 (57.8-80.8)	73.0 (58.9-82.9)	73.6 (60.1-84.7)	65.5 (45.9-77.9)	**0.003**
Male (%)	546 (59.3)	63 (52.5)	42 (58.3)	91 (53.5)	0.492
Residential or nursing care home resident (%)	51 (5.5)	10 (8.3)	4 (5.6)	10 (5.9)	0.979
WHO Performance Status ≥2 (%)	138 (15.0)	25 (20.8)	9 (12.5)	26 (15.3)	0.561
COPD (%)	244 (26.5)	39 (32.5)	16 (22.2)	39 (22.9)	0.903
Ischaemic heart disease (%)	145 (15.8)	25 (20.8)	11 (15.3)	25 (14.7)	0.510
Diabetes mellitus (%)	130 (14.1)	17 (14.2)	13 (18.1)	22 (12.9)	0.318
Cerebrovascular disease (%)	103 (11.2)	11 (9.2)	17 (23.6)	16 (9.4)	**0.003**
Asthma (%)	102 (11.1)	11 (9.2)	10 (13.9)	26 (15.3)	0.779
Congestive cardiac failure (%)	74 (8.0)	12 (10.0)	6 (8.3)	8 (4.7)	0.269
Active malignancy (%)	67 (7.3)	6 (5.0)	3 (4.2)	9 (5.3)	0.712
Dementia (%)	32 (3.5)	3 (2.5)	11 (15.3)	7 (4.1)	**0.002**
Mean Charlson co-morbidity index (95% CI)	1.48 (1.37-1.59)	1.68 (1.35-2.01)	1.97 (1.47-2.47)	1.36 (1.12-1.59)	0.036
Influenza vaccination in preceding 12 months (%)	558/855 (65.3)	76/114 (66.7)	41/62 (66.1)	98/154 (63.6)	0.729
PPV in preceding 10 years (%)	383/824 (46.5)	57/108 (52.8)	26/60 (43.3)	61/148 (41.2)	0.779
Severity					
PSI Class I-III (%)	395 (42.9)	42 (35.0)	30 (41.7)	78 (45.9)	
PSI Class IV (%)	336 (36.5)	48 (40.0)	23 (31.9)	58 (34.1)	0.545
PSI Class V (%)	189 (20.5)	30 (25.0)	19 (26.4)	34 (20.0)	
Outcome					
30-day mortality (%)	92 (10.0)	12 (16.7)	12 (16.7)	10 (5.9)	**0.035**
LOS	7 (4-12)	7 (4-11)	7 (4-11)	6 (4-10)	0.307
IRVS (%)	82 (8.9)	7 (9.7)	7 (9.7)	21 (12.4)	0.567

*P value compares VT with NVT serotypes. PPV: adult pneumococcal polysaccharide vaccine; LOS: length of hospital stay; IRVS: need for intensive respiratory or vasopressor support; VT: serotypes included within the 7-valent childhood pneumococcal vaccine (4, 6B, 9V, 14, 18C, 19F, 23F); NVT: serotypes not included within the 7-valent childhood pneumococcal vaccine; COPD: chronic obstructive pulmonary disease; CI: confidence interval; WHO: World Health Organisation; PSI: pneumonia severity index; IQR: interquartile range.

Table 6.1: Characteristics and outcomes of the study cohort.

	Whole cohort (n=920)	VT (n=72)	NVT (n=170)	Adjusted OR (95% CI)	P value*
Pleural effusion (%)	209 (22.7)	14 (19.4)	58 (34.1)	0.5 (0.3-1.0)	**0.050**
Multi-lobar involvement (%)	284 (30.9)	27 (37.5)	51 (30.0)	1.3 (0.7-2.4)	0.384
WCC ≥12 $x10^9$/l	579 (62.9)	47 (65.3)	118 (69.4)	0.9 (0.5-1.7)	0.736
CRP ≥100 mg/l (%)	523/826 (63.3)	44/67 (65.7)	112/159 (70.4)	0.9 (0.5-1.7)	0.479
Confusion (%)	120 (13.0)	21 (29.2)	28 (16.5)	1.6 (0.8-3.3)	0.174
RR ≥30 min^{-1} (%)	152 (16.5)	13 (18.1)	32 (18.8)	0.7 (0.4-1.6)	0.436
SBP <90 mmHg (%)	82 (8.9)	4 (5.6)	29 (17.1)	0.2 (0.1-0.8)	**0.017**

*P value compares VT with NVT serotypes. VT: serotypes included within the childhood pneumococcal vaccine (4, 6B, 9V, 14, 18C, 19F, 23F); NVT: serotypes not included within the childhood pneumococcal vaccine; IQR: interquartile range; CRP: C-reactive protein; SBP: systolic blood pressure on admission. Data on CRP are presented for only those who had this tested on admission.

Table 6.2: Clinical features for the study cohort.

Individual serotypes

Pneumonia caused by serotype 1 was associated with younger age (median age: 58.3 years, IQR 39.5-70.6, versus 73.0 years IQR 58.9-82.9; p<0·001) and less co-morbidity (mean Charlson co-morbidity index: 0.98, 95% CI 0.54-1.41, versus 1.68, 95% CI 1.35-2.01; p=0·012) compared with untyped pneumococcal disease (table 6.3; figure 6.1). Serotype 1 pneumonia was also associated with higher rates of para-pneumonic effusion (adjusted OR 2·6, 95% CI 1·2-5·8, p=0·016) and a higher proportion of patients with admission C-reactive protein (CRP) levels ≥100 mg/l (89·2% versus 65·7%; adjusted OR 3·6, 95% CI 1·1-11·1, p=0·028) (table 6.4). None of the 40 patients with serotype 1 CAP died within 30 days of admission (table 6.5). Similarly, serotype 7F pneumonia was associated with younger patient age (median age 45.8 years, IQR 32.8-75.8; p=0·013) and less co-morbidity (mean Charlson co-morbidity index: 0.71, 95% CI 0-1.45; p=0·013), and no patient deaths.

Serotype	n	Median age, years (IQR)	Male, n (%)	Charlson index, mean (95% CI)	PS ≥2 (%)
1	40	58.3 (39.5-70.6)	21 (52.5)	0.98 (0.54-1.41)	3 (7.5)
3	20	78.2 (66.9-86.7)	10 (50.0)	2.35 (1.63-3.07)	5 (25.0)
4	13	67.6 (52.8-84.2)	5 (38.5)	2.15 (0.48-3.82)	1 (7.7)
5	18	70.7 (58.7-82.1)	11 (61.1)	1.67 (0.70-2.63)	1 (5.6)
6A/C	11	78.3 (70.5-82.2)	6 (54.5)	1.82 (0.23-3.40)	4 (36.4)
7F	14	45.8 (32.8-75.8)	9 (64.3)	0.71 (0-1.45)	0 (0)
8	35	60.5 (44.0-75.8)	15 (42.9)	1.14 (0.79-1.50)	8 (22.9)
14	45	77.3 (67.0-84.5)	30 (66.7)	2.13 (1.50-2.76)	7 (15.6)
19A	20	71.1 (55.1-80.0)	10 (50.0)	1.25 (0.65-1.85)	2 (10.0)
Untyped	120	73.0 (58.9-82.9)	57 (48.3)	1.68 (1.35-2.01)	25 (20.8)

CI: confidence interval; IQR: interquartile range; PS: performance status.

Table 6.3: Demographic features by serotype.

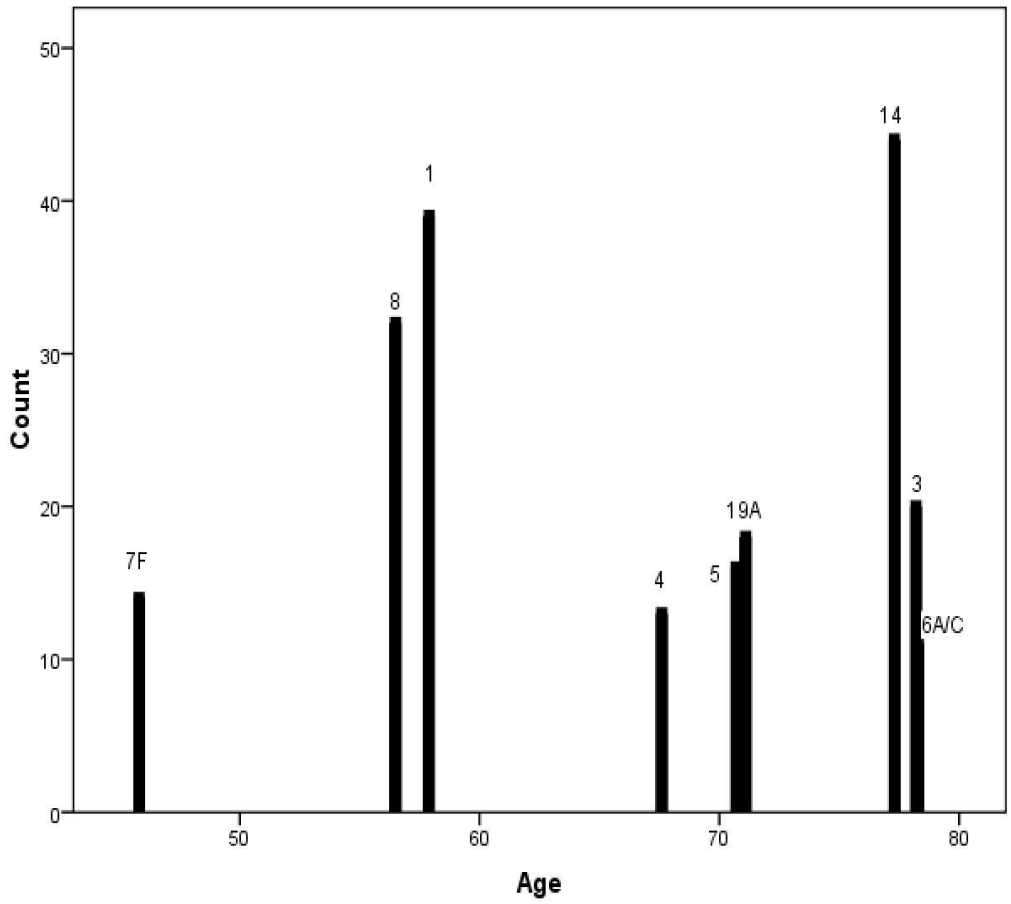


Figure 6.1. Distribution of serotypes according to median age and count within the cohort.

Serotype	n	Pleural effusion (%)	Multi-lobar involvement (%)	WCC, $x10^9$/l (IQR)	CRP, mg/l (IQR)	Confusion (%)	RR, min^{-1} (IQR)	SBP <90 mmHg (%)
1	40	18 (44)	9 (23)	17.6 (12.1-25.5)	286 (188-446)	5 (12.5)	24 (20-26)	6 (15)
3	20	8 (40)	7 (35)	13.3 (9.8-17.6)	77 (43-162)	4 (20.0)	24 (22-32)	2 (10)
4	13	3 (23)	4 (31)	10.7 (9.3-17.7)	127 (41-256)	2 (15.4)	23 (19-26)	1 (8)
5	18	6 (31)	6 (38)	13.6 (10.7-19.0)	99 (56-188)	3 (16.7)	21 (19-25)	5 (28)
6A/C	11	1 (9)	4 (36)	15.8 (12.2-19.4)	121 (65-167)	3 (27.3)	18 (16-23)	3 (27)
7F	14	3 (21)	4 (29)	16.9 (12.0-23.9)	288 (176-443)	0 (0)	20 (19-28)	1 (7)
8	35	11 (31)	10 (25)	17.5 (11.5-25.3)	173 (64-317)	4 (11.4)	21 (16-28)	5 (14)
14	45	8 (18)	20 (43)	14.3 (10.3-19.7)	171 (61-268)	13 (28.9)	22 (20-27)	2 (4)
19A	20	9 (45)	7 (33)	14.7 (11.9-21.5)	184 (106-261)	3 (15.0)	20 (18-26)	6 (30)
Untyped	120	27 (24)	37 (30)	15.6 (11.0-20.5)	155 (78-249)	14 (11.7)	24 (20-30)	14 (12)

WCC: white cell count; CRP: C-reactive protein; RR: respiratory rate; SBP: systolic blood pressure; VT: serotypes included within the childhood pneumococcal vaccine (4, 6B, 9V, 14, 18C, 19F, 23F); NVT: serotypes not included within the childhood pneumococcal vaccine. Data on CRP are presented for only those who had this tested on admission. Values are medians unless otherwise stated.

Table 6.4: Clinical features by serotype.

Serotype	n	Died by 30 days	Case fatality rate, % (95% CI)	LOS, days (IQR)	IVRS (%)
1	40	0	0 (0, 8.8)	7 (4-10)	4 (10.0)
3	20	2	10.0 (1.2, 31.7)	9 (5-14)	3 (15.0)
4	13	3	23.1 (5.0, 53.8)	7 (3-12)	1 (7.7)
5	18	1	5.6 (0.1, 27.3)	6 (5-11)	3 (16.7)
6A/C	11	1	9.1 (0.2, 41.3)	7 (5-14)	4 (36.4)
7F	14	0	0 (0, 23.1)	5 (4-9)	1 (7.1)
8	35	1	2.9 (0, 14.9)	5 (3-8)	5 (14.3)
14	45	7	15.6 (6.5-29.4)	9 (5-13)	3 (6.7)
19A	20	3	15.0 (3.2, 37.9)	5 (4-14)	0 (0)
Untyped	120	13	10.8 (5.9-17.8)	7 (4-12)	14 (11.7)

LOS: length of hospital stay; IRVS: need for respiratory or vasopressor support; IQR: interquartile range; CI: confidence interval, binomial, exact.

Table 6.5: Disease outcome by serotype.

In contrast, patients with serotype 3 pneumonia had higher levels of co-morbidity than the untyped pneumococcal group (p=0·028). Serotype 6A/C was associated with an increased need for IRVS (36·4%, adjusted OR 4·3, 1·1-16·9, p=0·034), and serotype 19A pneumonia was associated with para-pneumonic effusion (adjusted OR 2·8, 95% CI 1·1-7·7, p=0·039). Serotype 19A was also associated with a higher proportion of patients who were hypotensive on admission (systolic blood pressure <90mmHg: adjusted OR 3·6, 95% CI 1·1-11·6, p=0·035), as was serotype 5 (adjusted OR 3·6, 95% CI 1·0-12·9, p=0·049). These statistically significant associations between serotype and clinical features persisted after adjustment for PSI instead of age and co-morbidity (table 6.6).

After adjusting for age, serotype 14 was significantly associated with cerebrovascular disease (OR 2.7, 95% CI 1.0-6.9; p<0.05) and dementia (OR 10.7, 95% CI 2.5-46.0; p=0.001), serotype 3 with diabetes mellitus (OR 3.3, 95% CI 1.1-9.6; p<0.05), and serotype 8 with asthma (OR 3.8, 95% CI 1.4-10.0; p=0.008) (table 6.7).

Association	PSI adjusted OR (95% CI)	P value
NVT serotype with admission SBP <90mmHg	4.6 (1.5-14.1)	**0.008**
NVT serotype with pleural effusion	2.3 (1.1-4.4)	**0.018**
NVT serotype with PPV vaccination	1.0 (0.5-1.9	0.954
Serotype 1 with pleural effusion	3.1 (1.5-6.8)	**0.004**
Serotype 1 with CRP >100mg/l	4.2 (1.4-12.9)	**0.011**
Serotype 6A/C with IRVS	4.5 (1.1-18.7)	**0.037**
Serotype 19A with pleural effusion	3.1 (1.1-8.2)	**0.027**
Serotype 19A with admission SBP <90mmHg	4.7 (1.4-15.5)	**0.012**
Serotype 5 with admission SBP <90mmHg	3.1 (0.9-11.1)	0.075

OR: odds ratio; NVT: serotypes not included within the childhood pneumococcal vaccine; CRP: C-reactive protein; IRVS: intensive respiratory or vasopressor support; SBP: systolic blood pressure.

Table 6.6. Associations presented in the text, adjusted for Pneumonia Severity Index rather than age and co-morbidity

Serotype	n	Active malignancy (%)	COPD (%)	Asthma (%)	Dementia (%)	CVA (%)	DM (%)	CCF (%)
1	40	2 (5.0)	8 (20.0)	6 (15.0)	0 (0)	2 (5.0)	2 (5.0)	1 (2.5)
3	20	1 (5.0)	6 (30.0)	3 (15.0)	3 (15.0)	3 (15.0)	7 (35.0)	2 (10.0)
4	13	2 (15.4)	3 (23.1)	2 (15.4)	1 (7.7)	2 (15.4)	1 (7.7)	0 (0)
5	18	1 (5.6)	4 (22.2)	3 (16.7)	0 (0)	0 (0)	2 (11.1)	2 (11.1)
6A/C	11	2 (18.2)	2 (18.2)	0 (0)	1 (9.1)	1 (9.1)	3 (27.3)	1 (9.1)
7F	14	1 (7.1)	3 (21.4)	0 (0)	0 (0)	1 (7.1)	2 (14.3)	0 (0)
8	35	0 (0)	7 (20.0)	11 (31.4)	2 (5.7)	4 (11.4)	4 (11.4)	0 (0)
14	45	1 (2.2)	11 (24.4)	6 (13.3)	9 (20.0)	11 (24.4)	12 (26.7)	4 (8.9)
19A	20	1 (5.0)	5 (25.0)	3 (15.0)	0 (0)	4 (20.0)	2 (10.0)	2 (10.0)
Untyped	120	6 (5.0)	39 (32.5)	11 (9.2)	3 (2.5)	11 (9.2)	17 (14.2)	12 (10.0)

COPD: chronic obstructive pulmonary disease; CVA: Cerebrovascular disease; DM: diabetes mellitus; CCF: congestive cardiac failure.

Table 6.7. Distribution of co-morbidity by serotype.

Bacteraemic patients

Of the 40 patients with pneumococcal bacteraemia, 35 were of NVT serotypes compared with three VT serotypes (OR 6·0, 95% CI 1·8-20·0, p=0·001) (table 6.8). In one patient no serotype was available, and in a second patient the Bio-Plex and blood culture serotypes were different (serotype 15A from blood culture and 18C from Bio-Plex). The proportion of VT serotypes within the bacteraemic patients was significantly lower than in the non-bacteraemic patients (3/38 (7·9%) versus 69/204 (33·8%), p=0·001). Bacteraemic patients did not have higher disease severity (by PSI) or worse disease outcomes compared to non-bacteraemic pneumococcal CAP patients (30-day mortality: 5.0% versus 11.0%; IVRS: 10.0% versus 9.5%; p>0·2 for each). Bacteraemia was associated with lower rates of influenza and pneumococcal polysaccharide vaccination, but this difference was not maintained after adjusting for age (pneumococcal vaccination: OR 0·7, 95% CI 0·3-1·8, p=0·461; influenza vaccination: OR 0·7, 95% CI 0·3-1·4, p=0·299).

	Bacteraemic (n=40)	Non-bacteraemic (n=326)	P value
VT (%)	3 (7.5)	69 (21.2)	**0.040**
PSI Class I-III (%)	21 (52.5)	130 (39.9)	
PSI Class IV (%)	11 (27.5)	121 (37.1)	0.296
PSI Class V (%)	8 (20.0)	75 (23.0)	
30-day mortality (%)	2 (5.0)	90 (11.0)	0.281
IRVS (%)	4 (10.0)	78 (9.5)	0.805
Influenza vaccination in the preceding 12 months (%)	14/34	205/300	**0.002***
Pneumococcal vaccine in the preceding 10 years (%)	8/33	139/287	**0.008***

*:statistically significant association was not maintained after adjusting for age (see text). IRVS: need for respiratory or vasopressor support; PSI: pneumonia severity index; VT: serotypes included within the childhood pneumococcal vaccine (4, 6B, 9V, 14, 18C, 19F, 23F); NVT: serotypes not included within the childhood pneumococcal vaccine.

Table 6.8: Univariate analysis comparing pneumococcal bacteraemic and non-bacteraemic patients.

Serotypes of lower prevalence

The study has so far concentrated on serotypes with a number ≥10 within the cohort. The clinical features for the other serotypes (n<10) are presented in tables 6.9 to 6.12. As the numbers of each individual serotype are low, statistical comparison is not possible. However, these data are included within the VT or NVT groups as appropriate in the previous analyses.

Serotype	n	Median age, years	Male, n (%)	Charlson index, mean (95% CI)	PS ≥2 (%)
18C	4	71.5	3	1.00	0
12F	2	66.3	2	1.00	1
15A+18C	1	90.7	1	2.00	0
19F	3	65.1	1	1.00	0
22F	3	79.1	3	1.33	1
33F	3	50.6	2	2.00	1
35F	1	89.5	0	2.00	0
4+8	3	77.5	1	0.67	1
6B	2	87.9	1	1.50	1
6B+9V	1	34.1	0	0	0
9V	4	60.2	2	2.00	0
28F	1	37.7	1	1.00	0
35B	1	86.7	1	5.00	0
9N	1	34.9	0	0	0

CI: confidence interval; PS: performance status.

Table 6.9. Demographic features by serotype.

Serotype	n	Active malignancy (%)	COPD (%)	Asthma (%)	Dementia (%)	CVA (%)	DM (%)	CCF (%)
18C	4	0	0	1	0	2	0	1
12F	2	0	1	0	0	0	0	0
15A	1	0	0	0	0	0	1	0
19F	3	0	0	0	0	0	0	0
22F	3	0	2	0	0	1	0	0
33F	3	1	0	0	1	0	0	0
35F	1	0	0	0	0	0	0	0
4+8	3	0	0	0	0	1	1	0
6B	2	0	0	0	1	1	0	0
6B+9V	1	0	0	0	0	0	0	0
9V	4	0	2	1	0	1	0	1
28F	1	0	0	0	0	0	0	0
35B	1	0	1	0	0	0	0	0
9N	1	0	0	0	0	0	0	0

COPD: chronic obstructive pulmonary disease; CVA: Cerebrovascular disease; DM: diabetes mellitus; CCF: congestive cardiac failure.

Table 6.10. Distribution of co-morbidity by serotype.

Serotype	n	30-day mortality	LOS, days	IVRS
18C	4	1	6.5	1
12F	2	1	6	1
15A	1	0	10	0
19F	3	0	6	0
22F	3	0	15	0
33F	3	0	4	0
35F	1	0	9	0
4+8	3	0	25	1
6B	2	1	12.5	0
6B+9V	1	0	3	0
9V	4	0	5	2
28F	1	0	11	0
35B	1	1	6	0
9N	1	0	10	0

LOS: length of hospital stay; IVRS: need for respiratory or vasopressor support.

Table 6.11. Disease outcome by serotype.

Serotype	n	Pleural effusion (%)	Multi-lobar involvement (%)	CRP, mg/dl	WCC, x10^9/l	Haemoglobin, g/dl	Temperature, °C	RR, min^{-1}	Pulse, min^{-1}	SBP, mmHg
18C	4	0	0	111	11.9	14.1	37.3	28	96	132
12F	2	0	1	305	8.0	14.1	37.8	33	102	159
15A	1	0	0	399	17.8	11.6	36.8	15	61	218
19F	3	1	1	267	11.8	12.1	37.8	20	90	110
22F	3	0	1	171	18.0	13.9	37.5	28	111	138
33F	3	1	1	268	19.2	13.0	38.3	22	91	116
35F	1	0	0	362	17.0	11.8	36.2	16	87	138
4+8	3	1	1	500	21.2	12.8	36.6	20	74	111
6B	2	0	1	396	15.0	14.1	38.7	29	127	142
6B+9V	1	1	0	450	22.0	11.3	39.2	26	136	126
9V	4	1	1	120	20.4	11.9	37.6	22	115	140
28F	1	0	0	20	13.3	11.7	37.9	18	170	80
35B	1	0	0	17	18.9	13.0	38.8	36	145	190
9N	1	1	1	268	1.1	15.0	38.6	30	140	100

Admission variables are described, and presented as median values. CRP: C-reactive protein; WCC: white cell count; RR: respiratory rate; SBP: systolic blood pressure.

Table 6.12. Clinical features by serotype.

Discussion

This is the first study to demonstrate differences in clinical features and outcomes according to pneumococcal serotypes in adults with both non-invasive and invasive pneumococcal CAP. These findings are likely to be more representative of adult pneumococcal pneumonia than studies based solely on IPD.

Important differences were noted in the clinical disease and characteristics of the patients infected with VT versus NVT serotypes. Infection with NVT serotypes was associated with a younger, fitter population, with lower adjusted 30-day mortality, but higher prevalence of shock on admission and para-pneumonic effusions. Observational data from IPD cohorts in children,[194, 198, 201] and adults,[194, 202] have indicated a recent shift towards NVT serotypes after introduction of the childhood pneumococcal conjugate vaccine. Changes in clinical presentation due to PCV-7-induced changes in serotype distribution have not been observed to date in adults. However, in children an increase has been documented in the incidence of empyema in the USA from 2·2 per 100,000 to 3·7 per 100,000 following the introduction of PCV-7,[205] primarily caused by NVT serotypes 1, 3 and 19A.[207] An increase in necrotizing pneumococcal CAP from 13% pre-PCV-7 to 33% post-PCV-7 has been observed in children in Utah, accompanied by an increase from 47% to 88% of NVT serotypes.[131] Our results suggest that a shift towards NVT serotypes could potentially mean fewer cases of pneumococcal CAP in the most vulnerable adults (those of older age and those with higher levels of co-morbidity) as well as a reduction in pneumococcal related mortality. This would be an added and unexpected benefit of childhood pneumococcal vaccination. However, there may also be an increase in the incidence of more complicated CAP in younger adults.

Serotypes 1 and 7F were associated with CAP in younger patients with lower levels of co-morbidity. These findings are similar to four studies confined to adult IPD that consistently found that serotypes 1 and 7F were associated with younger and fitter patients.[106, 108, 110] A correlation between the invasive potential of serotypes and the

pattern of clinical disease has been postulated to explain these observations. Thus, serotypes with greater invasive potential, such as 1 and 7F, may be more likely to cause primary disease in younger, previously fit patients, whereas serotypes with low invasive potential, such as 6A, colonise older patients with higher levels of co-morbidity, thereby acting as 'opportunistic' pathogens.[108]

However, the definition of invasive potential across serotypes is mostly based on studies comparing nasopharyngeal carriage with IPD rates in *children* or *infants.*[113-115] Serotypes with high invasive potential identified in this way include serotypes 1, 4, 5, 7F and 9V. In contrast, serotypes 3, 6A, 6B, and 15 have been consistently described as being less invasive. The only study to examine invasive potential and include adults used a similar methodology to generate case-carrier ratios for IPD. That study identified serotype 8 as having the highest ratio.[103] Serotypes 1, 5, 7F were not represented at all in adult carriage, implying high case-carrier ratios, while serotypes 3, 4 and 9V had intermediate case-carrier ratios. The serotypes identified in the current study based on their association with different clinical features and outcomes of CAP are strikingly similar to serotype groups identified by studies of invasive potential. This supports the concept of correlations between capsular type, invasive potential and disease characteristics.

The proportion of VT serotypes isolated in the bacteraemic cases within the current cohort was significantly lower than for the non-bacteraemic cases. For example, VT serotype 14 was the most prevalent serotype within the cohort, but in none of these cases was bacteraemia detected; in contrast, ten (25%) cases of NVT serotype 1 pneumonia were bacteraemic. This finding suggests that reliance on studies of IPD for a surrogate estimate of the serotype distribution for invasive and non-invasive pneumococcal CAP may underestimate the proportion of cases of VT serotype CAP, and that further surveillance using non-culture based methods is needed.

Of the urine specimens from patients who tested negative using Binax NOW®, 144 had a pneumococcal serotype detected by Bio-Plex. Binax NOW® remains a useful and rapid means of identifying pneumococcal infection, but these results suggest that a negative result should not be used to exclude pneumococcal disease.

As of April 2010 PCV-7 was replaced in the UK paediatric immunisation schedules with a 13-valent pneumococcal conjugate vaccine (PCV-13). This contains (in addition to the types in PCV-7) serotypes 1, 3, 5, 6A, 7F, and 19A, all of which have been shown in our study to contribute to CAP in adults. Ongoing culture and non-culture surveillance of pneumococcal CAP is essential to determine the impact of PCV-13 on adult pneumococcal CAP presentations and outcomes.

Study limitations

Many of the limitations are similar to those described in the previous chapter. This study had limited power to detect differences in clinical features of individual serotypes due to the small numbers involved. Additionally, despite adjustment for potential confounding variables, the observed clinical differences between individual serotypes or groups of serotypes may nevertheless be residually confounded. Attempts have been made to minimise this potential limitation using two models for most analyses: a) adjusting for age and co-morbidity alone, and b) adjusting for disease severity using the well-validated Pneumonia Severity Index which includes age, co-morbid illness and clinical factors. The consistency of results in both models adds to the reliability of the associations observed.

Conclusion

Pneumococcal serotypes are associated with different clinical patterns for both invasive and non-invasive adult CAP and there are clear differences in clinical outcomes. A higher proportion of NVT serotypes represented in adult CAP through a shift in serotype distribution caused by the introduction of the childhood pneumococcal

conjugate vaccine may lead to lower overall 30-day mortality, but also a higher hospitalised population of younger patients with low levels of co-morbidity.

Chapter 7: The effect of child contact on adult pneumococcal disease

“Exogenous infections arise by direct contact with a patient suffering from pneumonia, or with a carrier…”

“Diseases of the Chest”, Dr Robert Coope (1944)

Introduction

As discussed in chapter 2, pneumococci are spread by contact between infected persons or with asymptomatic carriers, especially children with nasopharyngeal colonisation. However, to date studies have only investigated the transmission of pneumococcal *carriage* between children and adults, and the role contact with children plays in the development of adult pneumococcal disease has not been elucidated.

The previous chapter has shown considerable differences between the characteristics of pneumococcal CAP in adults between different serotypes. However, it is not known whether these differences may be explained by factors intrinsic to the pneumococcal serotype or predisposing features of the host. For example, are serotypes 1 and 7F seen more frequently in disease in younger adults because of some characteristic feature specific to these serotypes, or are younger adults exposed to (and therefore develop infection with) more NVT serotypes because they are more likely to have young children in the household, who in turn are more likely to carry these NVT serotypes post PCV-7 vaccination?

This study aims to a) test the hypothesis that contact with a vaccinated child could result in prospectively more non-vaccine type (NVT) adult pneumococcal CAP, b) to assess the impact of vaccination of child contacts with the 7-valent childhood pneumococcal vaccine (PCV-7) on serotype in adult CAP, and c) to explore the link between changes in the epidemiology of vaccine-type (VT) disease in adults and contact with PCV-7 vaccinated children.

Methods

A questionnaire (see appendix 3) was completed for each of the patients recruited in the cohort study as described in chapter 4. Contact with children was estimated by

patient or relative interview at the time of recruitment. Close social contact was defined as living in the same household as a child or spending more than eight hours in the company of a child in the four weeks preceding admission. If such contact was present, child demographic details were requested from the participant. If of an appropriate age, data concerning PCV-7 vaccination were obtained from primary care vaccination records via the regional Health Protection Agency. Participants where vaccination data were available for child contacts were split into three groups:

- group A, contact with a PCV-7 vaccination child;
- group B, contact with an unvaccinated child aged ≤8 years;
- group C: no child contact preceding admission.

A "child" is defined as a person aged ≤8 years, but further analyses were performed for contacts aged ≤5 years.

Statistical analysis

Statistical calculations were made using SPSS v16.0 (©SPSS Inc., 1989-2007). Differences between continuously distributed and categorical variables were analysed using Mann-Whitney U test and Pearson's χ^2 respectively. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using Pearson's χ^2 when performing univariate analysis. A p value of less than 0.05 was taken to represent statistical significance.

The association between child contact and pneumococcal CAP or individual serotypes were assessed using a logistic regression model, with adjustment made for age (with groups representing ages 16-49, 50-64, 65-74, 75-84 and 85+ years) and co-morbidity (as measured by the Charlson co-morbidity index,[389] grouped into no (score 0), mild (1-2), moderate (3-4) or severe (5+) co-morbidity), or pneumonia severity using the Pneumonia Severity Index (PSI). The "adjusted odds ratios" quoted in the text are following adjustment for age and co-morbidity unless otherwise stated. In

comparisons between individual serotypes, the untyped group was used as the comparator.

Results

Of 1099 patients identified with CAP during the study period, 956 patients consented to be included in the study. Thirty-six patients were unable to provide a urine sample, and full data on child contacts were not available in a further 52, leaving 868 for analysis.

Child contact and risk of pneumococcal CAP

The demographic profiles of these two groups are shown in table 7.1. Significant differences were found between participants who did and did not have close social contact with children ≤8 years with regards to age, co-morbidity and outcome, with child contact being associated with younger age and less co-morbidity. A higher proportion of women had preceding close contact with a person ≤8 years than men (136/357 (38.1%) vs. 126/511 (24.7%); OR 1.9, 95% CI 1.4-2.5, p<0.001). Of the 262 (30.2%) patients who had close social contact with a child ≤8 years in the four weeks preceding admission, 225 had contact with a child aged ≤5 years.

	Child contact (n=262)	No child contact (n=606)	P value
Median age (IQR)	60.5 (43.5-75.6)	74.9 (65.2-84.1)	**<0.001**
Male (%)	166 (50.5)	362 (64.4)	**<0.001**
Median LOS (days)	5 (3-9)	8 (4-13)	**<0.001**
30-day mortality (%)	12 (4.6)	70 (11.6)	**0.001**
IVRS (%)	19 (7.3)	56 (9.2)	0.338
Care home (%)	0 (00)	49 (8.1)	**<0.001**
PPV	92/245 (37.6)	274/544 (50.4)	**0.001**
Influenza vaccination	138/253 (54.5)	397/565 (70.3)	**<0.001**
COPD (%)	60 (22.9)	172 (28.4)	0.094
Asthma (%)	41 (15.6)	56 (9.2)	**0.006**
Cerebrovascular disease (%)	22 (8.4)	73 (12.0)	0.114
CCF (%)	12 (4.6)	59 (9.7)	**0.011**
Active cancer (%)	13 (5.0)	49 (8.1)	0.101
Dementia (%)	1 (0.4)	28 (4.6)	0.001
Diabetes mellitus (%)	31 (11.8)	93 (15.3)	0.143
Mean CCI (95% CI)	1.18 (1.00-1.35)	1.62 (1.48-1.76)	**<0.001**
Pneumococcal aetiology	123 (46.9)	223 (36.8)	**0.005**

A “child” is defined as a contact aged ≤8 years. IVRS: need for invasive respiratory or vasopressor support; IQR: interquartile range; LOS: length of hospital stay; CC: critical care; PPV: polysaccharide pneumococcal vaccine; COPD: chronic obstructive pulmonary disease; CCF: congestive cardiac failure; CCI: Charlson co-morbidity index; CI: confidence interval.

Table 7.1 Demographic comparison of patients with confirmed CAP with and without preceding child contact.

Of 346/868 (39.9%) patients with pneumococcal CAP, a serotype was determined in 229 (66.2%). There was history of pre-admission child contact in 123/346 (35.5%) patients with pneumococcal CAP. Contact with children was associated with pneumococcal CAP when compared with non-pneumococcal or unknown aetiology (OR 1.5, 95% CI 1.1-2.0; p=0.005) (table 7.1). This statistically significant association was maintained after adjustment for age, adult pneumococcal vaccination status and co-morbidity (OR 1.6, 95% CI 1.1-2.2, p=0.006). Fourteen patients within the cohort worked with children on a daily basis; of these, seven (50%) had evidence of pneumococcal CAP. A serotype was determined for all seven patients; the most prevalent was serotype 1 (n=3), the others being one each of serotypes 8, 14, 9V and 19A.

Effect of childhood vaccination on adult VT disease

Infection with a VT serotype was present in 63/225 (28.0%) cases where a single serotype was determined (in the remaining four cases both a VT and NVT serotype were found concomitantly). Contact with any child ≤8 years or ≤5 years was not associated with the development of NVT disease (p=0.913 and p=0.889 respectively; table 7.2). However, contact with a *PCV-7 vaccinated* child was significantly associated with CAP due to NVT serotypes when compared to contact with a child aged ≤8 years who had not been vaccinated (group A versus group B: OR 2.7 95% CI 1.1-7.1; p=0.035). This association was maintained after adjustment was made for PSI class in a logistic regression analysis (OR 2.8, 95% CI 1.1-7.5; p=0.033), but not when adjusted for age and co-morbidity (OR 2.2, 95% CI 0.8-6.1; p=0.142). In this second analysis, neither age nor co-morbidity were significantly associated with NVT CAP (age group: OR 0.7, 95% CI 0.5-1.1; p=0.106; CCI group: OR 0.8, 95% CI 0.4-1.4; p=0.413).

	NVT serotype (%)	OR for VT CAP (95% CI)	P value
Contact age ≤8 years (n=88)	63 (71.6)	1.0 (0.5-1.8)	0.913
Contact age ≤5 years (n=73)	53 (72.6)	1.0 (0.6-1.9)	0.889
Group A: contact, vaccinated (n=54)	43 (79.6)	1	-
Group B: contact, unvaccinated (n=34)	20 (58.8)	2.0 (1.1-7.1)	**0.035**
Group C: no child contact (n=137)	99 (72.3)	1.5 (0.7-3.2)	0.294
Group B+C (n=171)	119 (69.8)	1.7 (0.8-3.6)	0.152

VT: serotype contained within PCV-7; NVT: serotype not contained within PCV-7; OR: unadjusted odds ratio; CI: confidence interval; CAP: community-acquired pneumonia.

Table 7.2. Comparison of child contact status with risk of developing NVT CAP for patients in whom a pneumococcal serotype was determined.

Association of contact with a PCV-7-vaccinated child with adult CAP serotype

The most prevalent serotypes in patients who had been in close social contact with PCV-7 vaccinated children were 1 and 7F, and the most prevalent in those with no prior contact with children were 3, 8, and 14 (table 7.3). After adjustment for age and co-morbidity, serotypes 1 and 7F were associated with higher rates of patient contact with vaccinated children compared with patients with untyped pneumococcal disease (group A versus group B and group C combined; $p<0.05$ for each serotype) (table 7.4). When limiting the analysis to group A versus group B (i.e. only patients who had close contact with children aged ≤8 years), serotype 1 was associated with contact with vaccinated children after adjustment for age and co-morbidity with borderline significance (OR 3.9, 95% CI 0.9-15.7; $p=0.059$).

	Serotype									
	1	**3**	**4**	**5**	**6A/C**	**7F/A**	**8**	**14**	**19A**	**Untyped**
	(n=38)	**(n=18)**	**(n=13)**	**(n=18)**	**(n=10)**	**(n=13)**	**(n=35)**	**(n=36)**	**(n=19)**	**(n=110)**
Group A: contact, vaccinated	18	2	2	2	3	7	5	4	6	15
Group B: contact, unvaccinated	4	1	3	2	0	1	9	8	2	12
Group C: no child contact	16	15	8	14	7	5	21	24	11	83
Groups B and C	20	16	11	16	7	6	30	32	13	95

VT: serotype contained within the 7-valent pneumococcal conjugate vaccine (4, 6B, 9V, 14, 18C, 19F 23F.

Table 7.3. Comparison of serotype distribution with child contact, including the nine most prevalent serotypes in the current cohort.

Serotype	OR	95% CI	P value
1	4.1	1.7-10.1	**0.002**
3	1.5	0.3-8.1	0.643
4	2.0	0.5-9.2	0.352
5	1.0	0.2-5.2	0.975
6A/C	4.2	0.9-20.5	0.077
7F/A	5.2	1.3-20.6	**0.020**
8	0.9	0.2-2.4	0.753
14	1.2	0.3-4.0	0.814
19A	3.1	0.9-10.2	0.065
Untyped	1	-	-
Age group	0.6	0.4-0.7	**<0.001**
CCI group	0.6	0.4-0.9	**0.015**

Odds ratios represent the odds of adult CAP with each serotype for patients with close social contact with a PCV-7-vaccinated child (group A) compared with patients with no contact with a vaccinated child (groups B and C combined).

OR: odds ratio compared with untyped pneumococcal CAP; CI: confidence interval; CCI: Charlson co-morbidity index.

Table 7.4. Multivariate analysis of the association of serotype with contact with a PCV-7-vaccinated child, after adjustment for age, co-morbidity.

Discussion

The main findings of this study may be summarised as follows:

a) Close social contact with children aged ≤8 years is an independent risk factor for pneumococcal CAP;
b) Contact with PCV-7 vaccinated children is associated with an increased severity-adjusted risk of NVT CAP when compared with patients who have close contact with an unvaccinated child;
c) The NVT serotypes 1 and 7F are particularly associated with prior contact with PCV-7-vaccinated children.

Child contact as a risk factor for adult pneumococcal CAP

A link between pneumococcal disease and contact with children has previously been indirectly demonstrated in a study by Nuorti and colleagues. In this study, 228 patients with invasive pneumococcal disease (IPD) were compared with 301 control subjects who were age- and sex- matched healthy members of the population.[38] The presence of children <6 years of age attending day care in the household of the index case was associated with a 3-fold increased risk of IPD. Association between day care attendance and development of IPD has also been seen in children,[390, 391] but this is the first study showing a direct link between adult pneumococcal CAP and contact with any children aged ≤8 years. A plausible mechanism for this effect is that as nasopharyngeal colonisation rates in children of this age are far higher than in adults, a significant mode of acquisition of pneumococci by adults is through contact with children, in contrast to other microbiological causes of CAP.

Child contact as a risk factor for NVT disease

Within the group of patients who have close contact with children, this study has shown that adult contacts are more likely to contract NVT pneumococcal CAP if they have contact with a child who has been vaccinated with PCV-7. This implies that the transmission of VT serotypes is reduced from children who have been vaccinated. This is supported by data showing a reduction in child nasopharyngeal carriage of VT

serotypes compared with unvaccinated children,[57, 185] and a subsequent reduction in carriage of VT serotypes by adult family contacts.[52, 58] However, no study has yet looked at the direct influence of contact with vaccinated children on adult VT disease rather than carriage. This study therefore adds to the knowledge concerning the mode of pneumococcal transmission and disease acquisition by adults.

The previous chapter has shown that NVT disease is associated with patients who are younger and fitter, but with a higher chance of pleural effusion and shock on admission. NVT serotypes have also been shown previously in adult IPD cohorts to be associated with low severity disease in younger people.[106, 108, 110, 392] However, it is not known whether this is due to factors intrinsic to the organism or serotype, or whether host factors are involved, or both. This study shows that child contact is a risk factor for NVT disease regardless of disease severity, but not when adjustment is made for age and co-morbidity (although a non-significant positive association is still seen). This suggests that, at least in part, the predisposition of younger and fitter patients to acquire NVT pneumococcal CAP as seen in the previous chapter is explained by the increased likelihood of contact with young children within this patient group.

Potential mechanisms for inter-serotype variation in acquisition

This study has suggested that not all NVT serotypes are equally associated with PCV-7 vaccinated child contact; serotypes 1 and 7F in particular show a clear association with contact with a vaccinated child, whereas other NVT serotypes prevalent within this cohort (notably 3, 5 and 8) shown no such association. The reasons behind this are unclear, but a number of mechanisms may contribute.

Prevalence within child disease

Since the introduction of PCV-7 there has been an increase in NVT serotypes in pneumococcal disease in children. However, not all NVT serotypes have increased by equal degree. In several recent child IPD cohorts, serotypes 1 and 7F have

conspicuously increased in prevalence when compared with other NVT serotypes.[201, 202, 393, 394] Conceivably, adult disease may be preceded by pneumococcal *disease* (rather than colonisation) in contact children, and by this means common serotypes in child disease have become more common in close adult contacts. Data on the health of the child at the time of contact within this cohort are not available, but would be an interesting area of future work.

Selective expansion of nasopharyngeal carriage prevalence

Serotypes 1 and 7F were very rare within carriage studies in children prior to introduction of PCV-7 (see table 2.4), but some more recent studies in PCV-7 vaccinated children have shown evidence of increasing prevalence.[57, 143] Vaccination may therefore be driving a selective increase in certain NVT serotypes, which is reflected in increased transmission and adult pneumococcal disease. To confirm or refute this hypothesis it would be necessary to obtain nasopharyngeal samples from child contacts of adults with CAP in whom the infecting pneumococcal serotype was known. This would be an interesting area for future work.

Variation in capsular thickness

It has previously been shown that pneumococcal capsular thickness correlates with risk of death, but inversely correlates with invasive potential,[121] which may explain why the serotype prevalence in IPD and carriage studies is markedly different. Serotypes 1 and 7F have particularly thin capsules.[395] This may have two implications. A thin capsule may promote development of disease following carriage; of all the NVT serotypes adults are exposed to during social contact with children, it may be these that preferentially progress to cause disease. Alternatively, their thin capsule, whilst hindering persistent *colonisation*, may predispose to *transmission* from child to adult, explaining the increased prevalence in contact adults.

Study limitations

Many of the limitations described in the preceding two chapters also apply to this study. In particular, the sub-group analyses presented in this chapter have relatively low numbers, and the results should therefore be interpreted with caution. In addition, child contact was ascertained by patient recall at the time of admission, and therefore may be subject to bias either in patients with severe disease, or imperfect recall of the weeks preceding the admission. The authors have omitted from analysis any participants who were unsure of the details of their child contacts, and any from whom inaccurate data on child contacts were supplied. However, the only rigorous way to confirm direct transmission from colonised child to adult contact would be to obtain rapid nasopharyngeal swabs from contact children of adults admitted with CAP, thereby confirming the presence of the same strain or serotype in both. This may be a useful area of future work.

Conclusion

Child contact is independently associated with pneumococcal disease, and contact with PCV-7 vaccinated children predicts infection with NVT serotypes independent of pneumonia severity, in particular serotypes 1 and 7F. This reinforces the mechanism of acquisition of pneumococcal pneumonia, and may inform future conjugate vaccine development.

Chapter 8: The value of symptom scoring on outcome

“He suddenly feels shivery and ill, and huddles in front of the fire looking grey and shocked…”

“Diseases of the Chest”, Dr Robert Coope (1944)

Introduction

Research in community-acquired pneumonia (CAP) requires reliable outcome measures by which clinical studies may be powered and efficacy of interventions compared. However, many of the routinely used outcome measures are flawed. Mortality is confounded by factors such as frailty, co-morbidity and age, and it has been estimated that deaths from CAP are attributable to the acute illness in only around half of patients.[281] Length of hospital stay (LOS) is a useful outcome to measure in patients with low severity CAP, but may be prolonged by physician practice,[363, 365, 396] and functional status pre-admission and during admission.[356, 364] Significant variability in LOS has also been demonstrated between different hospitals.[360, 361] Time to reach clinical stability, as defined by normalisation of a number of routinely measured physiological variables,[343, 344] approximates the effect of treatment on objective measures of disease such as respiratory rate, temperature and pulse rate. It has been correlated with LOS,[356] treatment failure, and CAP complications.[345]

However, morbidity due to CAP may persist long after clinical and radiological resolution, up to six months in some cases.[346-348] Respiratory symptoms and quality of life are rarely reported in CAP studies, despite being significant patient-centred outcomes. Measuring symptoms may also allow good estimation of the impact of an intervention in patients with low severity CAP, a group which by definition has a low rate of adverse outcomes. A recently derived symptom score ("CAP score")[352] has been shown to accurately map changes in symptoms between admission, days 3, 7, 10, 14, and at 6 week follow-up. It correlates with individual physiological variables and inflammatory markers, and may be divided into two components which reflect respiratory symptoms and general well-being respectively. However, the CAP score has yet to be validated in an external cohort, and it is not known whether it may be useful in detecting changes in symptoms on a daily basis.

The aim of this study was to validate the CAP score in an independent cohort of patients with CAP, in particular to: a) determine the association with physiological stability in the first few days following hospital admission; and b) to determine if improvements in symptom scores correlate with other clinical outcome measures.

Methods

Patient recruitment

A random sample of patients enrolled in the cohort study described in chapter 4 were recruited between January and June 2010. Patients were included if they met the inclusion criteria for the cohort study, and were not confused (and therefore unable to accurately report symptoms) or too ill to answer the CAP score questionnaire. Eligible participants were approached on a daily basis for four days following admission and the CAP score questionnaire completed.[352] The score assigns points based on the presence or absence of breathlessness, cough, sputum, and general well-being (appendix 1), with a higher score denoting less severe symptoms (maximum score 100). A good symptomatic improvement between admission and day four was defined as a twenty point improvement in CAP score. This score can be sub-divided into two components, one describing the purely respiratory symptoms of breathlessness, cough, and sputum ("respiratory score") and the second describing general well-being ("well-being score"). Temperature, pulse rate, respiratory rate, blood pressure, and oxygen saturations with fraction of inspired oxygen (f_iO_2) were prospectively recorded from the first set of observations of the morning for each of the four days on which a symptom score was recorded. Participants who were discharged within four days from admission were excluded from analysis.

Definitions

"Clinical stability" was defined as the presence of heart rate <100 beats/min, systolic blood pressure >90 mmHg, respiratory rate <24 breaths/min, oxygen saturation >90% (and not using supplemental oxygen), and temperature <37.8°C. These criteria have been described elsewhere,[343, 344] and have been included in international guideline

statements.[1, 264] Pneumonia severity was estimated using the Pneumonia Severity Index (PSI).

Outcome measures

The clinical outcome measures assessed were death within 30 days of admission, re-admission within 30 days of discharge, and admission to a critical care area. An "adverse outcome" was defined as any one of these outcomes.

Statistical considerations

All statistical analyses were performed using SPSS v16.0 (©SPSS inc., 1989-2007). Categorical data were compared using Pearson's χ^2 test. Non-normally distributed continuous variables were compared using Mann-Whitney U test, or Kruskal-Wallis test when comparing the four consecutive days of symptom scores. Correlation of two non-normally distributed continuous variables was assessed using Spearman's rank correlation coefficient. A p value of <0.05 was taken as statistically significant. A logistic regression analysis was used to investigate the association between clinical stability and symptom score, with day of admission used as a co-variate.

Results

Over this study period 131 patients were admitted with CAP. Of these, 64 were eligible for inclusion, and 50 completed CAP scores for the four consecutive days following admission. Of the fourteen patients who did not complete four days of CAP scores, seven were discharged, four were lost to follow up, and three became too unwell to continue following recruitment. The median age of participants was 64.7 years (interquartile range (IQR) 44.9-75.5). Demographic and clinical features of the study cohort are shown in table 8.1. Thirty-five patients (70%) were classified by PSI into class I-III (low severity), 11 (22%) class IV (moderate severity), and 4 (8%) class V (high severity). Thirty-day mortality was 6% (n=3) and 8% (n=4) were admitted to a critical care area. Median LOS for survivors was 7 days (IQR 5-13).

Demographics	
Median age (years) (IQR)	64.7 (44.9-75.5)
Male (%)	24 (48)
COPD (%)	15 (30)
Asthma (%)	6 (12)
Other chronic lung disease (%)	4 (8)
CCF (%)	1 (2)
Current smoker (%)	10 (20)
PSI class	
I-III (%)	35 (70)
IV (%)	11 (22)
V (%)	4 (8)
Admission clinical variables	
Temperature °C, median (IQR)	37.4 (36.9-38.4)
Pulse rate min^{-1}, median (IQR)	112 (101-122)
Systolic blood pressure mmHg, median (IQR)	126 (104-139)
Respiratory rate min^{-1}, median (IQR)	24 (20-25)
C-reactive protein, median (IQR)	179 (32-300)

IQR: interquartile range; COPD: chronic obstructive pulmonary disease; CCF: congestive cardiac failure; PSI: pneumonia severity index.

Table 8.1. Clinical and demographic features of the study cohort.

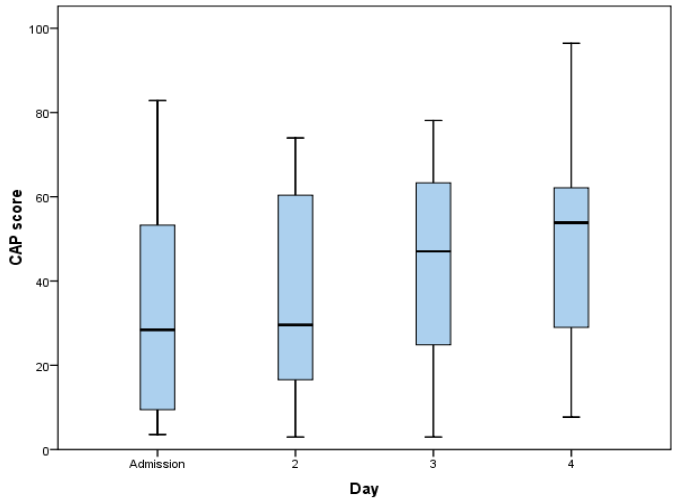
Change in symptom scores from admission and correlation with outcome

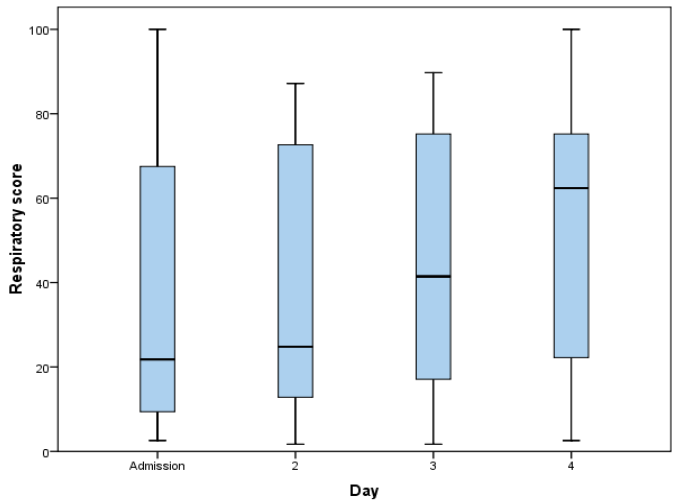
The CAP score and its two constituent component scores (the respiratory and well-being scores) had improved significantly by day four of admission (table 8.2, figure 8.1) ($p<0.05$ for all three scores). The well-being score improved rapidly compared with the respiratory symptom score, but reached a lower absolute level by day four. In eight patients the CAP scores were lower at day four than admission; half of these patients (n=4) were either admitted to critical care, were readmitted following discharge, or died within 30 days (table 8.3). In contrast, eighteen patients (36%) had an improvement in CAP score of more than twenty points between admission and day four; of these, none had an adverse outcome. Patients without an increase in CAP score of at least twenty points were more likely to suffer an adverse outcome (OR 1.9; 95% confidence interval (CI) 1.4-2.6, p=0.003). The magnitude of change in CAP and respiratory scores between admission and day four did not correlate with LOS (CAP score: correlation coefficient -0.083, p=0.578; respiratory score: correlation coefficient -0.063, p=0.673). In contrast, there was a trend towards a correlation in the improvement in well being score with LOS (correlation coefficient -0.255; p=0.084).

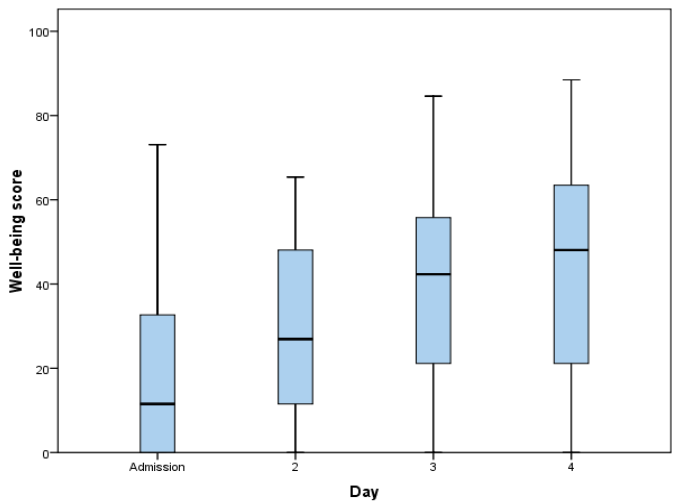
Day	CAP score (IQR)	Respiratory score (IQR)	Well-being score (IQR)
Admission	28.4 (9.5-53.4)	21.8 (9.4-68.4)	11.5 (0-33.7)
2	29.6 (16.1-60.7)	24.8 (12.6-73.3)	26.9 (11.5-48.1)*
3	47.0 (24.4-63.3)*	41.5 (17.1-75.2)	42.3 (21.2-55.8)*
4	53.8 (28.4-62.4)*	62.4 (21.4-75.2)*	48.1 (21.2-63.5)*

IQR: interquartile range; CAP: community-acquired pneumonia; *:p<0.01 compared with admission value.

Table 8.2. Changes in median symptom scores by day following admission.







Boxes represent median scores and interquartile ranges, with bars representing maximum and minimum scores.

Figure 8.1. Comparison of CAP score, respiratory score and well-being score over the first four days of admission.

	n	Died	Critical care	Readmission	Any adverse outcome (%)	Median LOS (IQR)
CAP score						
>20 point improvement	18	0	0	0	0 (0)	8 (4-11)
0-20 point improvement	24	2	3	4	8 (33)*	9 (6-13)
Deterioration	8	1	1	2	4 (50)*	5 (5-16)
Respiratory score						
>20 point improvement	13	0	0	1	1 (8)	7 (4-11)
0-20 point improvement	28	2	3	3	7 (25)	8 (5-13)
Deterioration	9	1	1	2	4 (44)*	5 (5-15)
Well-being score						
>20 point improvement	29	2	3	2	7 (24)	7 (5-9)
0-20 point improvement	18	1	1	2	4 (22)	9 (5-16)
Deterioration	3	0	0	2	2 (67)	14 (n/a)

*: $p<0.05$, χ^2 test compared with >20 point improvement group; IQR: interquartile range

Table 8.3. Comparison of change in symptom scores over the course of the admission with outcome.

Association with physiological and inflammatory parameters

Full physiological data for all four days of admission were missing for six patients (a total of 14/200 (7%) sets of observations). The presence of clinical stability was consistently associated with higher median symptom scores across all four days (table 8.4). When adjustment was made for day of admission using a logistic regression analysis, CAP score remained independently associated with clinical stability (OR 1.02, 95% CI 1.00-1.04; p=0.042). Of patients who were clinically stable by day four, 8/19 (42%) had also shown an increase in CAP scores by over twenty points, compared with 8/25 (32%) of patients who were not clinically stable (p=0.490). There were significant negative correlations between CAP score and respiratory rate, but not with temperature, heart rate or blood pressure (table 8.5).

	Clinically stable (n=38)	Clinically not stable (n=148)	OR (95% CI)	P value
Median CAP score (IQR)	52.7 (39.3-70.4)	35.8 (14.8-60.8)	1.03 (1.01-1.04)	**0.002**
Median respiratory score (IQR)	62.4 (34.2-76.5)	29.1 (12.8-72.7)	1.02 (1.01-1.03)	**0.004**
Median well-being score (IQR)	48.1 (25.5-57.7)	21.2 (11.5-48.1)	1.02 (1.01-1.04)	**0.006**

IQR: interquartile range; OR: odds ratio; CI: confidence interval.

Table 8.4. Distribution of symptom scores by clinical stability.

	Temperature	P value	HR	P value	RR	P value	SBP	P value
CAP score	-0.034	0.647	-0.095	0.196	-0.223	**0.002**	0.058	0.433
Respiratory score	-0.039	0.594	-0.043	0.557	-0.161	**0.029**	0.070	0.344
Well-being score	-0.013	0.866	-0.219	**0.003**	-0.315	**<0.001**	0.023	0.759

HR: heart rate; RR: respiratory rate; SBP: systolic blood pressure.

Table 8.5. Correlation between CAP, respiratory and wellbeing scores with physiological parameters.

C-reactive protein levels and PSI class were not correlated with CAP, respiratory or well-being scores at admission. Similarly, the CAP score did not correlate with any individual physiological parameter measured at the time of hospital admission, including temperature, respiratory rate, pulse or blood pressure.

Discussion

The principal finding of this study is that the CAP score at any stage within the first four days of hospital admission correlates with clinical stability. Failure of symptom scores to improve by at least twenty points is also associated with a higher incidence of adverse outcomes. In addition, changes in the CAP score were observable on a daily basis after admission with CAP, and symptom scores correlated with physiological parameters. These data suggest that the CAP score is a responsive and clinically relevant measure of response to treatment.

The use of symptom scoring as an outcome measure would have particular benefit in studies of low to moderate severity CAP, complementing traditional outcome measures of mortality, re-admission or critical care admission. The CAP score is difficult to use with patients with high severity CAP as very sick patients are unable to answer the relevant questions, and the presence of confusion also restricts its use. Symptom scores do however represent a meaningful patient-centred outcome, in contrast to physiological stability and may also be useful in the community by means of self-completed questionnaires.

In order for the CAP score to be useful as an outcome measure in clinical studies, it should correlate with other clinically relevant outcomes. This study has shown that clinical stability at any stage during the first four days of admission is associated with higher symptom scores (in other words, less frequent or severe symptoms). The

principal physiological marker that correlated with symptoms was respiratory rate, and to a lesser extent heart rate. The derivation study for this score showed strong links between improving symptoms and physiology,[352] but in contrast to the current study showed that temperature was a strong predictor of symptoms. This may reflect the relatively small samples sizes of both studies, and further larger studies may help to clarify this area. In addition this study also found a statistically significant association between the failure of symptom scores to improve by at least twenty points after admission with an adverse outcome comprising 30-day mortality, re-admission to hospital following discharge or admission to a critical care area. The respiratory component of the CAP score seemed to be more predictive than the well-being component, as deterioration in respiratory score was associated with adverse outcome, whereas deterioration in well-being score was not.

The well being score has the lowest absolute value of the scores at admission, rose at a faster rate during the first four days of admission, but did not reach the same level as the respiratory score by day four. This finding is in keeping with other published studies. El Moussaoui and colleagues followed patients up for six months after admission, and found that the well-being component of the CAP score took longer to resolve than the respiratory component.[348] Marrie and colleagues showed that fatigue was slower to resolve than any respiratory symptom such as cough or breathlessness.[347] This finding is relevant in that general well-being is perhaps the most important symptom for patients, but it is difficult to measure objectively with physiological or radiological parameters or clinical outcome measures, and is therefore not measured as an outcome in most CAP studies.

Study limitations

The main limitation with this study was the relatively small sample size with correspondingly small numbers of patients with high severity CAP. This precluded detecting a correlation with individual outcomes such as 30-day mortality. However, in our experience, the CAP score was less practically applicable in very ill patients. Therefore, validation of the CAP score in such patients will not necessarily be of value. While the CAP score is mainly of utility in patients with low and moderate severity CAP, this study took place in a hospitalised cohort, and the results are not applicable to a primary care population without further validation.

Conclusion

This study validates the CAP symptom score as a simple tool to monitor treatment response in the first few days of hospital admission that correlates with physiological parameters and other commonly used CAP outcomes. It may be of particular value in patients with low-moderate severity CAP.

Chapter 9: The value of oxygenation assessment in predicting outcome

"…Blood gas analysis…is not feasible in clinical work…Happily certain simple observations are sufficient; the appropriate (oxygen) dosage is that which provides relief of the cyanosis, restlessness and delirium, together with a fall in the pulse rate."

"Diseases of the Chest", Dr Robert Coope (1944)

Introduction

There remains substantial uncertainty regarding the role of pulse oximetry in the context of the CRB-65 score for disease severity assessment in patients presenting to primary care with CAP. In particular, there is uncertainty regarding the thresholds of S_pO_2 that are associated with clinically significant outcomes. The aims of this study were a) to assess the utility of different thresholds of S_pO_2 in predicting adverse outcomes in CAP; b) to assess the utility of low S_pO_2 as a prognostic tool in sub-groups such as the young and those without respiratory co-morbidity; and c) to compare the prognostic value of oxygenation assessment for mortality with existing clinical severity scoring.

The ideal study design to address these questions would be a large cohort study conducted in primary care with follow-through in the hospital. A sample size of several thousand would be required to capture enough patients with an adverse outcome (admission to critical care or death) to enable a robust analysis. There are major practical and feasibility hurdles in mounting such a large study. The current study design which focuses on a cohort of patients hospitalised with CAP has design limitations but still offers important and useful data that might inform further studies.

Methods

Patient population and recruitment

Patients for this analysis recruited in the prospective observational study (chapter 4) between September 2008 and February 2010. Demographic, co-morbidity and severity data were collected for all patients, and S_pO_2 levels with the fraction of inspired oxygen (F_iO_2) as first measured by the triage nurse team were documented.

Statistical considerations

The primary outcome measure was a combined end point of inpatient mortality within 30 days of admission or admission to a critical care area. Other outcomes examined were length of hospital stay (LOS) and need for mechanical ventilation (MV). Patients

were only included in the current study if the initial oxygen assessment was performed on room air.

Data were analysed using SPSS v16.0 (©SPSS inc., 2007). The association of S_pO_2 with the primary outcome measure was examined with and without adjustment for disease severity using a logistic regression analysis, from which odds ratios were calculated. Groups of patients were further analysed according to admission S_pO_2 thresholds commonly used in guideline statements (<88%, ≤90%, ≤92%, and <95%) using Pearson's χ^2 test, and measures of performance including sensitivity and specificity were calculated. Using the most suitable S_pO_2 threshold, patient sub-groups were compared in a similar manner. Continuous variables of other outcomes (such as LOS) were normalised logarithmically prior to analysis using Student's T test. The utility of CRB-65 as a predictor for 30-day mortality was analysed using receiver-operating characteristic (ROC) curves. A binary measure for each of the oxygenation thresholds was added to the individual CRB-65 scores and areas under the curve (AUC) calculated for each ROC curve.

Results

Patient population

Of 832 patients analysed, 365 received pre-admission supplemental oxygen and therefore did not have S_pO_2 levels measured on room air at the time of hospital admission, leaving 467 patients in the study cohort. Mean age was 66.7 years (standard deviation 20.1) and 30-day inpatient mortality was 10.3%. Further demographic and clinical features of the patient cohort are described in table 9.1.

Characteristic	Total	S_pO_2>90% (n=336)	S_pO_2≤90% (n=131)	p value
Mean age (years)	66.7	64.5	72.3	**0.001**
Male (%)	57.0	58.9	51.8	0.17
Care home resident (%)	12.6	9.8	19.8	**0.003**
Clinical features				
Dyspnoea (%)	88.2	87.2	96.7	0.35
Cough (%)	77.4	75.2	83.7	0.08
Productive sputum (%)	59.4	56.6	67.3	0.06
Fever ≥38.0°C on admission (%)	37.3	36.1	40.2	0.43
Co-morbid illness				
COPD (%)	17.8	13.7	28.2	**0.001**
Asthma (%)	9.9	11.9	4.6	**0.001**
CVD (%)	14.2	14.0	14.6	0.86
Dementia (%)	8.1	6.3	13.0	**0.017**
Chronic renal impairment (%)	7.5	7.4	7.6	0.94
Active malignancy (%)	7.1	6.0	10.0	0.13
CCF (%)	6.9	5.1	11.5	**0.014**
Chronic liver disease (%)	1.3	1.8	0	0.13
Oxygenation				
Median S_pO_2 (IQR) (%)	94 (90-96)	95 (93-96)	87 (82-89)	**<0.001**
CRB-65 risk class (%)				
0	131 (28.1)	116 (34.5)	15 (11.5)	<0.001
1	186 (39.8)	129 (38.4)	57 (43.5)	
2	119 (25.5)	76 (22.6)	43 (32.8)	
3	31 (6.6)	15 (4.5)	16 (12.2)	
4	0 (0)	0 (0)	0 (0)	
Miscellaneous				
Mean haemoglobin (SD)	12.7 (1.9)	12.8 (1.9)	12.5 (2.0)	0.22
Mean urea (SD)	10.1 (10.5)	9.8 (11.2)	10.7 (8.3)	**0.03**
Mean creatinine (SD)	120 (96)	118 (83)	123 (100)	0.45

S_pO_2: capillary oxygen saturations; SD: standard deviation; COPD: chronic obstructive pulmonary disease; CCF: congestive cardiac failure; CVD: cerebrovascular disease. Symptoms exclude those who were unable to communicate through confusion or disease severity.

Table 9.1. Patient demographics.

Utility of different thresholds of S_pO_2 in predicting adverse outcomes

S_pO_2 measured at the time of admission was found on univariate analysis to be inversely associated with the combined outcome of 30-day mortality and critical care admission (per unit decrease in S_pO_2, odds ratio (OR) 1.09, 95% confidence interval (CI) 1.05-1.14, p<0.001). This association was maintained after adjustment for disease severity using the CRB-65 score (CRB-65 0 or 1, OR 1.11, 95% CI 1.05-1.17, p<0.001; CRB-65 2 and above, OR 1.06, 95% CI 1.00-1.11, p=0.04). All four commonly used thresholds for hypoxaemia were associated with poorer outcomes (table 9.2). There was a statistically significant association between decreasing thresholds of S_pO_2 and incidence of adverse outcome (for each decrease in threshold, OR 1.42, 95% CI 1.22-1.66, p<0.001). S_pO_2 ≤90% was found to have moderate discriminatory value (specificity >75%) while still applying to a reasonable proportion of patients (131/467, 28%). This threshold was therefore chosen for further analysis.

	Died/CC (%)	OR	95% CI	p value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
S_pO_2 <88% (n=69)	36.2	3.3	1.9-5.7	**<0.001**	29.8	88.5	36.2	85.2
S_pO_2 ≤90% (n=131)	29.8	2.7	1.7-4.5	**<0.001**	46.4	76.0	29.8	86.6
S_pO_2 ≤92% (n=187)	26.7	2.6	1.6-4.3	**<0.001**	59.5	64.2	26.7	87.9
S_pO_2 <95% (n=271)	22.5	2.2	1.3-3.7	**0.003**	72.6	45.2	22.5	88.3

CC: critical care; OR: odds ratio; CI: confidence interval; S_pO_2: percentage of capillary haemoglobin saturated with oxygen; PPV: positive predictive value; NPV: negative predictive value.

Table 9.2. Sensitivities and specificities for 30-day inpatient mortality or critical care admission by thresholds of hypoxaemia.

Utility of S_pO_2 ≤90% as a prognostic tool in sub-groups

The specificity of S_pO_2 ≤90% as a predictor of mortality or critical care admission was improved when applied to sub-groups of patients, in particular those aged less than 50 years (90.0%) and in patients with asthma (92.3%) (table 9.3). S_pO_2 ≤90% was a less reliable predictor in patients admitted from nursing or residential homes and those with chronic obstructive pulmonary disease. In patients with S_pO_2 ≤90%, admission to critical care, need for mechanical ventilation and LOS were each significantly increased (table 9.4).

	Died or CC (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
All (n=467)	18.0	46.4	76.0	29.8	86.6
Age <65 (n=179)	14.5	50.0	87.6	38.5	91.2
Age <50 (n=92)	13.0	41.7	90.0	38.5	91.1
Age <65 and no COPD (n=161)	13.7	40.9	87.9	34.6	90.5
COPD (n=83)	18.1	53.3	57.4	21.6	84.8
Asthmatic (n=46)	15.2	42.9	92.3	50.0	90.0
Care home resident (n=59)	27.1	56.3	60.5	34.8	78.8

CC: critical care; PPV: positive predictive value; NPV: negative predictive value; COPD: chronic obstructive pulmonary disease.

Table 9.3. Value of S_pO_2 ≤90% in predicting mortality or critical care admission in subgroups of patients with CAP.

	S_pO_2 >90% (n=336)	S_pO_2 ≤90% (n=131)	p value
Inpatient death by 30 days (%)	6.8	19.1	**<0.001**
Critical care admission (%)	7.4	15.3	**0.01**
MV (%)	1.8	5.3	**0.04**
Median LOS in days (IQR)	6.56 (8.54)	9.75 (10.33)	**<0.001**

CC: admission to any critical care area. MV: mechanical ventilation. LOS: length of hospital stay.

Table 9.4. Value of low oxygen saturations in predicting outcome.

Comparison of the prognostic value of S_pO_2 ≤90% with existing severity scoring

The area under the curve (AUC) of the receiver-operating characteristic (ROC) curve for CRB-65 in predicting 30-day inpatient mortality in this cohort was 0.768. When the binary measure of S_pO_2 ≤ or >90% was added the AUC was not substantially improved (0.785). For patients with low to moderate severity CAP based on a CRB-65 score of 0 or 1, S_pO_2 was ≤90% in 20/41 (48.8%) of those who subsequently died or were admitted to critical care. The sensitivity of CRB-65 ≥1 and ≥2 in predicting 30-day mortality in this cohort was 97.9% and 70.8% respectively, but was only 52.1% for S_pO_2 ≤90%.

Discussion

This study explored the utility of pulse oximetry in predicting outcome for patients admitted to hospital with CAP. Increasing levels of hypoxaemia were found to be significantly associated with higher odds of either 30-day mortality or critical care admission, even after adjustment for disease severity using the CRB-65 score. This is consistent with findings from a US CAP cohort that also demonstrated an association between low S_pO_2 levels measured on admission and a higher 30-day mortality and incidence of admission to critical care.[309] Compared to other threshold levels of hypoxaemia, S_pO_2 ≤90% was found in a significant proportion of patients admitted with CAP (28%) whilst retaining a reasonably good specificity (76%) for 30-day mortality or critical care admission. The specificity for adverse outcomes was particularly good when applied to patients with asthma (92%) and those who were <50 years (90%).

Proposed practical use of pulse oximeters

Measures of S_pO_2 are increasingly being utilised by general practitioners as the “fifth vital sign”.[397] Various possible interpretations of this sign are that “high” S_pO_2 levels might be reassuring in a patient who would otherwise cause clinical concern, or that “low” S_pO_2 levels predict higher severity and therefore need for admission to hospital.

The results from this study suggest that a threshold of S_pO_2 ≤90% may be used to "rule in" high severity CAP, even in patients that do not meet the high severity criteria of clinical scores such as CRB-65. This would apply especially to younger patients, those with asthma, or those without pre-existing significant lung disease. However, the poor sensitivity of hypoxaemia in the identification of patients at risk of adverse outcomes means that pulse oximetry cannot be relied upon as the sole means of severity assessment in CAP. In particular, it means that it is not possible to "rule out" an adverse outcome in a normoxaemic patient with CAP. Instead, clinical severity scores such as CRB-65 should remain the primary method for severity assessment of CAP in primary care, with pulse oximetry used as a secondary measure to inform clinical judgment in those patients who are of clinical concern in the face of a CRB-65 score of 0 or 1.

Mechanism of the association of hypoxaemia with adverse outcomes

These data suggest that hypoxaemia should be considered separately to variables such as blood pressure, mental confusion and respiratory rate which are incorporated into CRB-65. The latter variables are closely linked to systemic disease and sepsis (and therefore mortality) whereas hypoxaemia is a disease- and organ-specific measure, primarily of the level of shunt within the lungs. Physiological variables such as pulse, blood pressure and respiratory rate are unaffected by substantial hypoxaemia in healthy volunteers,[312] and correction of hypoxaemia has no influence on outcome either in a post-operative setting,[313] or in moderately hypoxaemic patients with CAP treated with continuous positive airways pressure (CPAP).[314] This may reflect the oxygen dissociation curve, which suggests that oxygen delivery to the tissues is only compromised at levels of S_pO_2 that are far lower than those associated with hypoxaemia as recognised within current practice. Therefore it may not be hypoxaemia *per se* that contributes to the adverse outcome, but that low S_pO_2 levels allow identification of the sub-group of patients who have severe single organ disease that falls short of influencing the sepsis-driven variables identified by most current severity scores. In patients with chronic respiratory disease such as COPD, there is

significant pre-existing ventilation/perfusion mismatch which means that hypoxaemia is a feature of “normal” physiology. Thus in these patients, a low S_pO_2 is not necessarily an acute pathological feature (in contrast to confusion, high respiratory rates or hypotension), and might explain why hypoxaemia was found to be less discriminatory for clinical outcomes.

Study limitations

This study was performed in an exclusively hospitalised cohort of patients and therefore raises questions regarding the applicability of these data to a primary care population. However, only patients whose admission S_pO_2 values were recorded on room air were studied and it is likely that these values would have been similar to values that might have been obtained in a primary care environment. In addition, a wide range in S_pO_2 levels, disease severity and clinical outcomes were represented in the study cohort. These features further increase the potential generalisation of the results. We are unable to comment on those patients with CAP who were not admitted to hospital, and a further study involving such patients is warranted. This study also allows no comment to be made concerning the value of pulse oximetry in discriminating pneumonic from non-pneumonic lower respiratory tract infection. A separate study in a cohort with *suspected* CAP, which will potentially include patients with non-pneumonic lower respiratory tract infection as well as other diagnoses, is also of great interest and would be important to enable the results of the current study to be applied more widely.

Conclusion

S_pO_2 ≤90% has good specificity but low sensitivity for adverse outcomes in CAP, and therefore complements rather than replaces clinical severity scoring tools. It is particularly useful in patients with asthma or younger patients who do not have chronic respiratory disease.

Chapter 10: Validation and augmentation of severity assessment scores

“With the pathological background in mind the student must try to translate the symptoms and signs which are present into a picture of what is happening – the extent, intensity, and stage of the disease.”

“Diseases of the Chest”, Dr Robert Coope (1944)

Introduction

Severity scoring for CAP is a key part of the admission process.[1, 264] The CAP severity scores in widest use currently are summarised in chapter 2. The pneumonia severity index (PSI),[266] CURB-65, and CRB-65,[285] have been widely validated in a multitude of international cohorts, with the newer SMART-COP and SMRT-CO less so. However, the demographic distribution of patients admitted to hospitals is changing, with levels of age and co-morbidity increasing, incurring a rising mortality.[9] Therefore existing severity scores may underestimate the effect on mortality of the increasing levels of frailty within the population of patients with CAP. Pre-admission functional status as measured by the Katz index,[398] and Barthel score has been independently associated with mortality.[399, 400] Additionally, CURB-65 was originally derived from a population excluding patients admitted from care homes, a population that make up a considerable proportion of medical admissions with CAP.

The aims of this study are to a) validate the scores CURB-65, CRB-65 and PSI for predicting 30-day mortality in a new cohort of patients to ensure ongoing clinical utility; b) to validate the newer SMART-COP and SMRT-CO for predicting the need for intensive respiratory or circulatory support in a UK patient cohort; and c) to incorporate a measure of baseline functional status into CURB-65 to attempt to improve mortality prediction in a more frail population.

Methods

Patient recruitment

Data on the three severity scores were calculated in patients recruited in the prospective observational study described in chapter 4.

Definitions

Pneumonia severity by risk group is defined as per the most recent British Thoracic Society guidelines:[1]

- Low severity pneumonia: CRB-65 0, CURB-65 0 or 1, PSI classes I, II or III
- Moderate severity pneumonia: CRB-65 1 or 2, CURB-65 2, PSI class IV
- High severity pneumonia: CRB-65 3 or 4, CURB-65 3, 4 or 5, PSI class V.

Intensive respiratory or vasopressor support (IVRS) is defined as the need for invasive or non-invasive ventilation, or shock requiring the use of vasopressors for blood pressure support.[296] Baseline performance status (PS) was estimated by the study investigator at recruitment as described in chapter 4. A PS of 3 or 4 was incorporated as a binary variable into CURB-65, producing a six point score that was evaluated using ROC curve analysis.

Statistical considerations

All statistical analyses were performed using SPSS v16.0 (©SPSS Inc., 1989-2007). Categorical variables, such as mortality, were compared between severity groups using χ^2. Odds ratios for mortality were calculated on univariate analysis by comparing lowest severity group to each higher group in turn.

The performance of the severity scores under examination was assessed using receiver-operating characteristic (ROC) curves. These are plots of sensitivity vs. 1-specificity, typically of a clinical test for a given outcome.[401] A measure of the efficacy of the test is the area under the curve (AUC) of the resultant plot; an AUC of 1 reflects a perfect test, whereas an AUC of 0.5 suggests no predictive ability. It is generally thought that values of 0.8 or higher reflect a good value for a clinical prediction rule.

For the purposes of validation of SMART-COP and SMRT-CO, scores based on escalation to critical care, patients aged more than 65 years were excluded from the analysis. The reason for this is that patients above this age are less likely to be admitted to critical care or be deemed appropriate for mechanical ventilation, or inotropic or vasopressor support, which conceivably could reduce the efficacy of the

score. In a number of patients oxygenation data were not available as an arterial blood gas sample was not performed (n=529).

Results

Cohort demographics

One thousand and ninety-nine patients admitted with CAP were included in this analysis. Full data for the three severity scores were available in 1088 (99.0%) patients; admission observations were unavailable in eight cases, haemoglobin not measured in one case, and blood urea not measured on admission in two cases. The mortality for the cohort was 14.6%. Mean age was 69.7 years (95% confidence interval (CI) 68.6-70.8), and median age was 73.6 years (interquartile range (IQR) 59.6-83.5). 12.7% patients were admitted to a critical care area. 144 (13.2%) patients were admitted from a nursing or residential home.

Comparison of the CURB-65, CRB-65 and PSI

The distribution of patients for each severity score class is shown in table 10.1. In all cases, higher severity CAP was associated with higher 30-day mortality, with odds ratios reaching statistical significance for each increasing risk group. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for predicting 30-day mortality are presented for the high severity groups for each score in table 10.2. CURB-65 ≥3 had the best sensitivity for 30-day mortality, but this value was still only 57.9%. The predictive values for CURB-65 ≥3 and PSI class V were very similar, with CRB-65 ≥3 less sensitive (28.9%) but more specific (93.2%).

Severity score class	N	Mortality (%)	OR (95%CI)	P value
CURB-65				
0	195	1 (0.5)	1	-
1	218	12 (5.5)		
2	356	54 (15.2)	5.5 (2.9-10.2)	**<0.001**
3	226	52 (23.0)		
4	83	36 (43.4)	12.5 (6.8-22.8)	**<0.001**
5	10	4 (40.0)		
CRB-65				
0	238	2 (0.8)	1	**-**
1	434	48 (11.0)	20.8 (5.1-84.7)	**<0.001**
2	307	63 (20.5)		
3	97	42 (43.3)	86.2 (20.4-364.6)	**<0.001**
4	12	4 (33.3)		
PSI				
I	103	1 (1.0)		
II	130	0 (0)	1	**-**
III	180	12 (6.7)		
IV	393	57 (14.5)	5.2 (2.8-9.7)	**<0.001**
V	282	89 (31.6)	12.1 (6.9-21.0)	**<0.001**
Total	1088	159 (14.6)	-	-

PSI: pneumonia severity index; OR: odds ratio for 30-day mortality; CI: confidence interval.

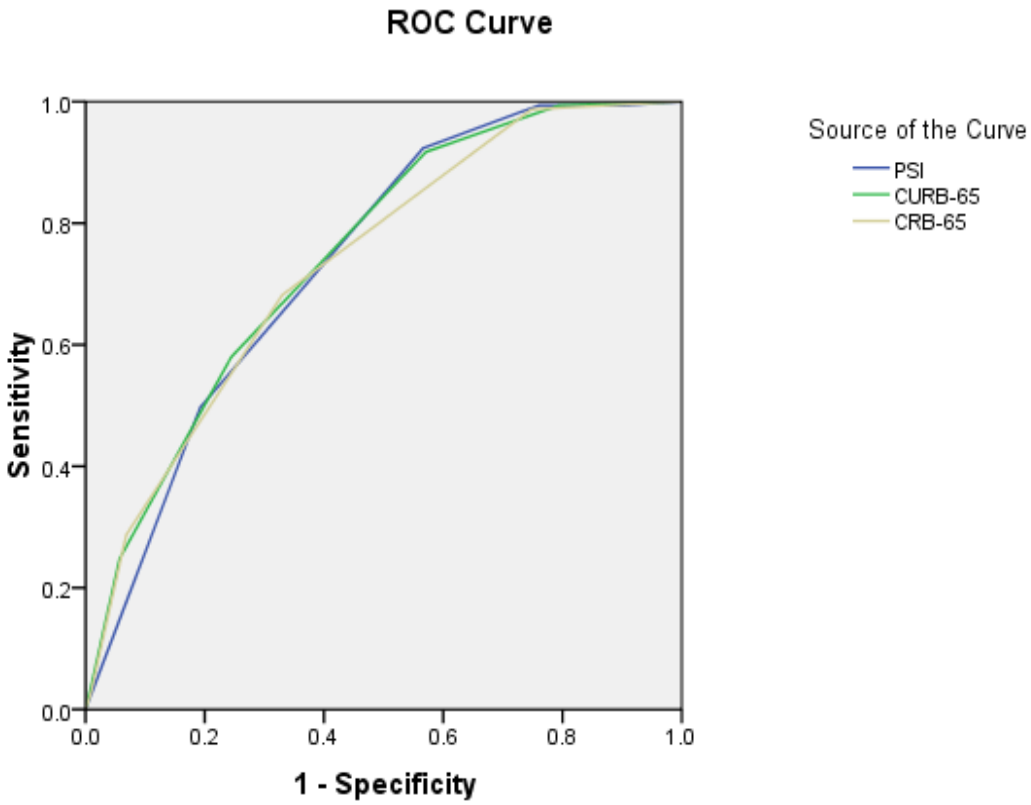
Table 10.1. Comparison of the distribution of severity score groups and mortality.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CURB-65 ≥3	57.9	75.6	28.8	91.3
CRB-65 ≥3	28.9	93.2	42.2	88.5
PSI class V	56.0	79.2	31.6	91.3

PSI: pneumonia severity index; PPV: positive predictive value. NPV: negative predictive value.

Table 10.2. Comparison of the characteristics of the high severity pneumonia groups in predicting 30-day mortality.

The ROC curves for each severity score are shown in figure 10.1. AUC's were of comparable magnitude for each severity score (PSI 0.747; CURB-65 0.748; CRB-65 0.738). Both CURB-65 and PSI classified 416 patients as low severity, compared with 238 for CRB-65. None of these severity scores adequately predicted the need for admission to a critical care area (ROC AUCs: PSI 0.585; CURB-65 0.575; CRB-65 0.551) or a combined endpoint of 30-day mortality or critical care admission (ROC AUC's: PSI 0.693; CURB-65 0.688; CRB-65 0.671).



	ROC AUC	95% CI
PSI	0.747	0.711-0.783
CURB-65	0.748	0.711-0.785
CRB-65	0.737	0.698-0.776

Figure 10.1. ROC curves and AUC for PSI, CURB-65 and CRB-65 in predicting 30-day mortality.

PSI: pneumonia severity index; ROC: receiver-operating characteristic curve; AUC: area under the curve; CI: confidence interval.

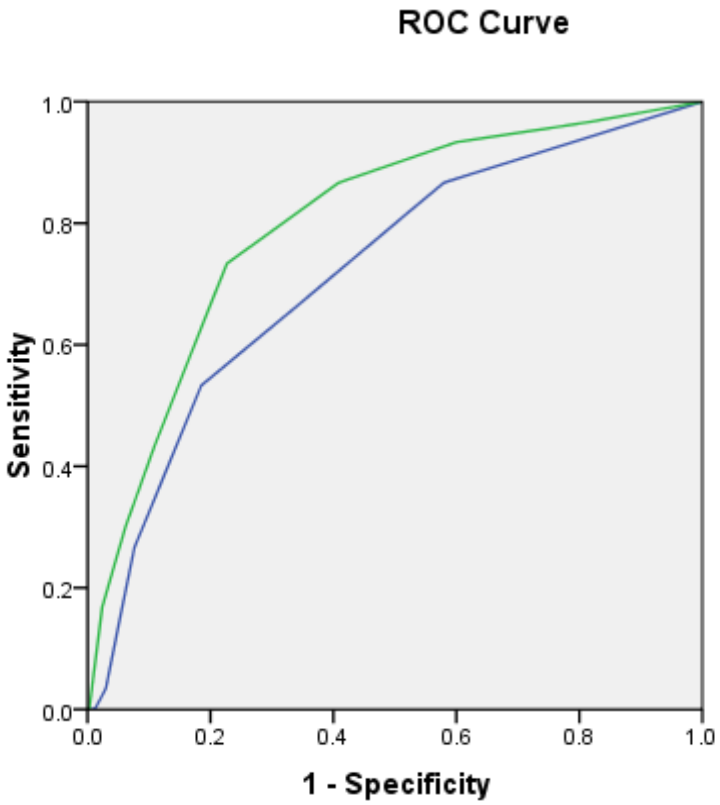
Validation of SMART-COP

SMART-COP (and its derivation SMRT-CO for use in primary care) were validated in those patients aged less than 65 years. 370 patients were available for analysis. The outcomes for each score point are shown in table 10.2, and the ROC curve for prediction of IVRS is shown in figure 10.2. AUC for the ROC curve of SMART-COP was 0.801, and for SMRT-CO was 0.719. The ROC AUC for predicting IVRS for CURB-65 in the same population was 0.617, and PSI 0.628. Both SMART-COP and SMRT-CO were inferior to CURB-65 in predicting 30-day mortality in the 370 patients aged ≤65 years (ROC AUC for CURB-65 0.798; for SMART-COP 0.620; for SMRT-CO 0.591).

SMART-COP score	n	IVRS (%)	30-day mortality (%)
0-2	205	4 (2.0)	4 (2.0)
3-4	115	13 (11.3)	3 (2.6)
5-6	37	8 (21.6)	2 (5.4)
≥7	13	5 (38.4)	1 (7.7)
SMRT-CO score			
0	147	4 (2.7)	2 (1.4)
1	86	6 (7.0)	3 (3.5)
2	58	4 (7.0)	2 (3.4)
3	45	8 (17.8)	1 (2.2)
≥4	34	8 (23.5)	2 (5.9)

IVRS: intensive ventilatory or vasopressor support.

Table 10.2. Distribution of patients as scored by SMART-COP and SMRT-CO.



		ROC AUC	95% CI
SMART-COP	--------	0.801	0.720-0.881
SMRT-CO	--------	0.719	0.624-0.814

Figure 10.2. ROC curves and AUC for the SMART-COP and SMRT-CO scores.

ROC: receiver-operating characteristic curve; AUC: area under the curve; CI: confidence interval.

Augmentation of CURB-65 using pre-admission performance status

Data on baseline PS were available on 1040 (95.6%) participants (table 10.3). Care home resident status was closely linked to PS (proportion of care home residents of patients at each PS level: PS 0, 2.2%; 1, 6.6%; 2, 34.3%; 3, 46.0%; 4, 68.6%). Incremental odds ratios for 30-day mortality were seen per point increase in performance status. PS of 2, 3, or 4 was strongly associated with increased 30-day mortality when compared with PS of 0 on univariate analysis (odds ratio 5.9, 95% CI 3.7-9.4; $p<0.001$). PS alone predicted 30-day mortality, with an AUC on ROC curve analysis of 0.695. Using a logistic regression model, PS predicted 30-day mortality independent of disease severity as measured by CURB-65, with each point increase in PS associated with a statistically significant rise in mortality (table 10.3). When PS ≥2 was incorporated into CURB-65 as a sixth predictor variable, the ROC AUC for 30-day mortality improved in this subset of 1040 patients from 0.741 to 0.761 (table 10.4).

			Univariate analysis		Multivariate analysis	
PS	**n**	**30-day mortality (%)**	**OR (95% CI)**	**P value**	**OR (95%CI)**	**P value**
0	496	31 (6.3)	1	-	1	-
1	317	46 (14.5)	2.5 (1.6-4.1)	**<0.001**	1.8 (1.1-2.9)	**0.024**
2	105	23 (21.9)	4.2 (2.3-7.6)	**<0.001**	2.4 (1.3-4.4)	**0.006**
3	87	26 (29.9)	6.4 (3.6-11.5)	**<0.001**	3.5 (1.9-6.5)	**<0.001**
4	35	15 (42.9)	11.3 (5.3-24.1)	**<0.001**	4.5 (2.0-10.2)	**<0.001**

Multivariate analysis represents PS adjusted for CURB-65 score as a single co-variate. PS: performance status; OR: odds ratio for 30-day mortality compared with PS=0; CI: confidence interval.

Table 10.3 Baseline performance status and 30-day mortality in a logistic regression analysis model.

	ROC AUC
All patients (n=1040)	
CURB-65	0.741
CURB-65 plus PS 2, 3 or 4	0.761
CURB-65 plus PS 3 or 4	0.759

PS: performance status; ROC: receiver-operating characteristic curve; AUC: area under the curve; NH: admitted from nursing or residential home.

Table 10.4. Performance of prediction rules incorporating performance status.

PS would be expected to be of more utility in predicting mortality in those patients with more severe disease (those with CURB-65 scores 2 and above). When applied as a “second step” after stratifying patients into severity groups with CURB-65, using PS cut-offs of ≥2 or ≥3 showed highest performance in patients with moderate severity CAP (table 10.5). In patients with moderate severity CAP, death within 30 days was 2.5 and 3.3 times more likely with PS of ≥2 and ≥3 respectively. Similarly, the absence of PS ≥2 in moderate or high severity CAP was associated with substantially decreased mortality (negative likelihood ratios of 0.44 and 0.55 respectively).

PS 2, 3, or 4 Severity	N	Died (%)	Sensitivity	Specificity	+LR	-LR
Moderate (CURB-65 2)	69	19 (27.5)	67.9	72.8	2.50	0.44
High (CURB-65 3-5)	120	45 (37.5)	75.0	45.3	1.37	0.55
PS 3 or 4 Severity						
Moderate (CURB-65 2)	40	15 (37.5)	28.8	91.3	3.31	0.78
High (CURB-65 3-5)	67	26 (38.8)	33.8	81.1	1.79	0.82

PS: WHO performance status; +LR: positive likelihood ratio; -LR: negative likelihood ratio.

Table 10.5. Use of performance status as a "second step" following assignment of patients to moderate and high risk groups.

Discussion

In this large UK CAP cohort CURB-65, CRB-65 and PSI adequately predict 30-day mortality, with similar efficacy to previous studies. CURB-65 and PSI have an almost equivalent predictive ability, with CRB-65 slightly less effective. These severity scores are not accurate at predicting the need for respiratory or circulatory support, a finding replicated in other published CAP cohorts.[276, 296] However, SMART-COP does predict IVRS with good efficacy, as does SMRT-CO to a lesser degree.

CURB-65 and PSI are both widely used in hospitalised patients, with the former more prevalent in the UK and the latter in North America. Calculation of PSI involves input of more variables than CURB-65 (20 compared with 5), and whilst this allows inclusion of more data in the generation of the score (in particular, co-morbidity) it renders calculation of the score cumbersome for use as a front door assessment tool when compared with CRB-65 or CURB-65. PSI has previously been shown to identify more patients as low severity than CURB-65 or CRB-65, which may be useful in informing safe discharge decision.[276] In this study, no such effect was seen (413 vs. 413 vs. 238).

A problem with tri-modal severity scoring highlighted by this cohort is the proportion of patients identified as moderate severity (CURB-65 2, 356; CRB-65 1 or 2, 741; PSI class IV, 393). Such classification neither identifies patients with high severity CAP (and therefore in need of consideration of escalation of treatment) or low severity CAP (and therefore suitable for consideration of discharge).The ideal score would classify as few patients in the intermediate group as possible; for this cohort, the best performing score in this regard is therefore CURB-65.

SMART-COP is poorly predictive of 30-day mortality, but predicts the need for IVRS well, in contrast to CURB-65 and PSI. The potential reasons for this may lie in the causes of the two outcomes under study. 30-day mortality is primarily determined by sepsis or co-morbidity, which are heavily represented either directly or as surrogate

variables in CURB-65 and PSI. By contrast, the need for IVRS is often determined by oxygenation status or respiratory failure, and may not be deemed appropriate in the subset of frailer patients admitted to hospital. The three main predictor variables in SMART-COP are acidosis, hypoxaemia and systolic hypotension. In a study by Mortensen and colleagues, only 38% of deaths within 30-days of admission with CAP were attributable to respiratory failure.[281] Furthermore, as discussed in chapter 9, oxygenation status on admission does not improve the predictive ability of existing severity scores for 30-day mortality. SMART-COP places heavier weighting on oxygenation status and circulatory failure, and this may explain the improved predictive ability of SMART-COP over CURB-65 and PSI for the need for IVRS; as it places no weight on co-morbidity or frailty, it poorly predicts 30-day mortality. In clinical practice there is a need to be able to accurately predict both 30-day mortality in all patients with CAP and the potential need for IVRS in those patients where it is appropriate. Therefore both CURB-65/PSI and SMART-COP are useful front-door tools which give the clinician different information about a patient and may be used effectively in parallel.

The predictive ability of SMART-COP for IVRS was only validated in this study in those patients aged less than 65 years. In one of the only other studies to externally validate SMART-COP the analysis was restricted to patients aged less than 50 years.[301] There are several reasons for this. Firstly, outcomes such as IVRS may be more relevant in a younger population where mortality is low (2.0% in those aged ≤65 years in this cohort). Secondly, older patients referred to hospital are more likely to have severe co-morbidity which makes mechanical ventilation or vasopressor support inappropriate. There are no firm guidelines on which patients are “appropriate” for management in a critical care setting, and policy varies greatly between different countries. A potential surrogate for marker for patients who are deemed inappropriate for escalation to a critical care area is the decision not to resuscitate in the event of a cardiopulmonary arrest. In this cohort, 192 (17.5%) of patients had a “do not resuscitate” form filled out within the first few days of admission, and of these 187

(97.4%) were aged more than 65 years. Thus the investigators feel justified in using this age as a cut-off.

CURB-65 includes no measure of frailty, which may have considerable relevance in the older population. The PSI does allocate points for patients admitted from a care home, but this is an inaccurate measure of premorbid status, and is given low weighting in the overall calculation of the score. The original CURB-65 derivation study excluded patients admitted from nursing homes, and therefore may have represented a less frail population. In this study we have shown a modest improvement in the performance of CURB-65 by incorporating baseline PS of 2, 3, or 4 as an additional binary variable, despite strong prediction of 30-day mortality independent of CURB-65. The magnitude of this improvement is such that it is difficult to justify recommending widespread changes to CURB-65. This may reflect the fact that PS strongly correlates with age, and therefore adds little beyond age to the existing severity score. Future studies may consider the use of other objective measures of frailty to investigate this issue further.

Performance status may be useful in stratifying patients after application of CURB-65, particularly in the group of moderate severity. By using a cut off of PS ≥2 for patients with CURB-65 2 CAP we have shown a higher post-test likelihood ratio for 30-day mortality of 2.5 times that of those with PS of 0 or 1, giving a mortality similar to that seen in high risk patients (CURB-65 3-5). To illustrate, patients with moderate severity CAP and PS ≥2 had a 30-day mortality of 27.5%, compared with 6.3% for those with PS 0 or 1. This has clinical utility in that it may be used to decide whether more intensive management (for example, using intravenous antibiotics) would be more appropriate in patients with a higher PS. Therefore PS is a straightforward bedside test that would seem to have immediate clinical utility.

Strengths and limitations

The strengths of the current study are that it contains relatively large numbers of patients compared with contemporary cohorts, and has a prospective methodology. However, there are a number of limitations. Firstly, arterial blood gas data were not available for roughly half of the patients; this means that the values for SMART-COP and SMRT-COP may have been underestimated. Whilst this highlights a significant problem with the routine use of this score in clinical practice, it is less likely that patients who were significantly hypoxaemic would not have had an arterial blood gas sampled, minimising this potential bias. Furthermore, this study population had a higher mortality and was of older age than other published cohorts investigating severity scoring in CAP. This may explain why the values for ROC AUC were at the lower end of that expected from other cohorts. Interestingly, in another large cohort study which found lower than expected AUCs for the common severity scores, a similarly older demographic was seen (Man and co-workers; mean age 72 years,[276] compared with Lim and co-workers; mean age 64 years.[285]

Conclusion

In this validation study, PSI, CURB-65 and CRB-65 all performed equally well in predicting 30-day mortality. SMART-COP was more accurate predicting the need for intensive respiratory or circulatory support, and is a useful tool for those patients for whom such intervention is appropriate. Addition of a binary measure of poor performance status to CURB-65 modestly improved performance of the score, but when used as a post-test assessment, can identify a sub-group of patients of moderate severity CAP that are at much higher risk of death.

Chapter 11: The effect of timing of first chest radiograph on outcome

“Radiology of the chest is a matter for the expert”

“Diseases of the Chest”, Dr Robert Coope (1944)

Introduction

In recent years controversy has surrounded the prognostic benefit conferred by early antibiotic treatment of CAP on arrival to hospital (see chapter 3 for a full discussion). A short time to first antibiotic dose (TFA) for patients hospitalised with CAP was initially suggested to decrease mortality,[315, 321] and later hospital length of stay (LOS),[317, 324, 356] findings which have since been vigorously disputed.[322, 325-328, 402, 403] A number of reports have also been published showing an increase in both the CAP misdiagnosis rate and the proportion of patients inappropriately administered antibiotics following the introduction of clinical care pathways advocating a short TFA in all patients with suspected CAP.[323, 329, 330]

Early diagnosis with chest radiograph is desirable for a number of reasons. It facilitates a confident, appropriate management approach and the early use of appropriate antibiotics and severity scoring. It should also prevent the over-diagnosis or misdiagnosis of CAP based on clinical signs alone.[7, 404, 405] The British Thoracic Society has recently recommended that a diagnostic chest radiograph should be performed in patients admitted with suspected CAP as promptly as possible following admission (preferably within four hours) and that antibiotics should be administered as soon as possible *after* radiographic confirmation of CAP.[1] However, there are no published data demonstrating that early diagnosis of CAP as measured by time to first chest radiograph (TXR) is associated with improved clinical outcome.

The aim of this study was to determine whether a short TXR in patients hospitalised with CAP is associated with shorter hospital LOS and more appropriate timing of antibiotic administration in relation to chest radiography.

Methods

Patient data

Data collected between September 2008 and June 2009 from the prospective observational study described in chapter 4 were analysed. For the purposes of this

analysis, patients were also excluded if they were admitted from a nursing home. The time of first chest radiograph was retrieved from Radiology Department computerised records (all chest radiographs are digitally stored together with the exact timing of the investigation). All chest radiographs were reviewed by the duty radiologist, and patients were excluded if the radiograph reports were not in keeping with CAP. The time of first antibiotic administration was prospectively determined by drug chart review during the admitting episode (the exact timing of first antibiotic dose is usually recorded by the health care professional administrating the drug(s)). The time to first chest radiograph (TXR) and the time to first antibiotic dose (TFA) were defined as the time from arrival to hospital to first chest radiograph and to first antibiotic dose respectively.

Data analysis and statistical considerations

The primary outcome measure was hospital LOS, and the secondary outcome measures were a) timing of antibiotic administration in relation to chest radiography, b) 30-day mortality and c) 30-day readmission rates. “Thirty-day mortality” was ascertained from computerised hospital records, and was defined as death within 30 days of admission. “Readmission” was defined as readmission to hospital for any reason within 30 days of discharge.

For the analyses of TXR and TFA in relation to outcome, data for TXR and TFA were converted to categorical variables using four hours as the threshold value. This threshold value was chosen to reflect the ‘four hour target’ of admission to treatment that is applied to all acute medical admissions in England and Wales. All non-normally distributed continuous data were transformed logarithmically prior to statistical analysis with Student’s t test. Categorical data were analysed using Pearson’s χ^2 test, or Fisher’s exact test if sample sizes were small. All analyses involving LOS excluded those that had died prior to hospital discharge.

A sample size of 500 patients would have 80% power to detect a fall in LOS of 1.26 days with a significance level of 5%. Assuming a mortality of 15% within the same population, a mortality difference of 7% would be required to achieve statistical significance with 80% power.

Results

Patient characteristics

Five hundred and forty-six patients were included in this analysis. Eighty-five patients were excluded for a variety of reasons (table 11.1), leaving 461 for analysis. Of these, 64 died in hospital and were not analysed for LOS. The median age of the study cohort was 72 years (range 17-102 years) and 60.7% were male. Median LOS for the entire cohort was 6.59 days (interquartile range (IQR) 9.45 days), mortality was 13.7%, and readmission rate was 16.2% for those patients who survived to discharge. Median TXR was 1.91 hours (IQR 3.60 hours), with 333 (72.2%) radiographs performed within four hours of admission and 236 (51.2%) within two hours. 49.8% patients received both their chest radiograph and antibiotics within four hours of arrival to hospital. For 35 patients there was uncertainty in the medical records regarding the exact time the first dose of antibiotic was administered, and these patients were therefore excluded from any analyses relating to TFA.

Reason	Number excluded
Patient admitted from a nursing home	74
Admitted directly from outpatient clinic	2
Exact time of admission unclear from clinical records	5
Chest radiograph performed by GP prior to hospital admission	4

Table 11.1. Distribution and explanation of patients excluded from analysis.

Comparison of groups

No differences in age, sex, performance status, or co-morbidity were found between patients with TXR ≥4 hours and TXR <4 hours (table 11.2). Patients with a TXR <4 hours were more likely to be short of breath (92.4% vs. 85.4%, p=0.052, odds ratio (OR) 2.1), but in other respects the prevalence of lower respiratory tract symptoms was not statistically different between these groups. There was a significantly lower rate of antibiotic use in the two weeks prior to hospital admission in patients with TXR <4 hours (30.1% vs. 41.7%; p<0.05). Patients with more severe disease (CURB-65 3-5) had a significantly shorter median TXR and TFA compared to patients with low severity CAP (CURB-65 0-1) (for TXR: 1.55 hours vs. 2.01 hours, p<0.05; for TFA: 2.80 hours vs. 3.67 hours, p<0.05). However, no difference in disease severity was noted between groups according to TXR of greater or less than four hours.

Characteristic	Survivors to discharge (n=397) TXR <4hours (n=291)	TXR ≥4hours (n=106)	p value
Demographics			
Median age (IQR) (years)	70 (26)	72 (23)	0.191
Male (%)	61.2	56.7	0.377
Mean smoking history in pack years (SD)	29.6 (33.1)	27.6 (24.2)	0.585
Proportion of admissions between 9am and 5pm (%)	46.0	48.1	0.715
Received antibiotics in the 2 weeks prior to admission (%)	30.1	41.7	<0.05
Admitted to a critical care area (%)	11.2	14.8	0.388
Symptoms			
Fever ≥38.0°C (%)	40.9	36.2	0.398
Productive cough (%)	66.0	62.9	0.601
Short of breath (%)	92.4	85.4	0.052
Confused (%)	18.6	21.7	0.484
Severity			
CURB-65 score 0-1 (%)	43.3	45.3	0.750
CURB-65 score 2 (%)	32.3	34.0	
CURB-65 score 3-5 (%)	24.4	20.8	
Co-morbidity			
Airways disease (%)	27.5	19.8	0.120
Cerebrovascular disease (%)	11.7	18.9	0.065
Active neoplasia (%)	6.2	9.4	0.263
Heart failure (%)	5.5	8.5	0.278
Renal disease (%)	6.2	4.7	0.580
Liver disease (%)	1.0	0.9	0.938
At least one of the above co-morbidities (%)	45.0	43.4	0.774
Admission performance status 3 or 4 (%)	49.1	46.2	0.959
Baseline performance status 3 or 4 (%)	3.2	5.8	0.452

Symptom data exclude those patients who were unable to communicate at admission. TXR: time from admission to first chest radiograph; SD: standard deviation; IQR: interquartile range.

Table 11.2. Characteristics of patients admitted to hospital with CAP who survived to discharge according to TXR.

Outcome measures

Median LOS was significantly shorter for patients with a TXR <4 hours compared to TXR ≥4 hours (5.75 days vs. 7.13 days; p<0.01) (table 10.3) and TFA <4 hours compared to TFA ≥4 hours (5.63 days vs. 8.07 days; p<0.01). Forty-four (9.5%) patients were hypotensive on admission (SBP<90mmHg). As these patients might have been treated differently from the other patients, a sub-analysis was performed with these patients excluded. In this sub-analysis, the association of TXR <4 hours with a reduced median LOS was maintained (5.63 days vs. 7.01 days, p<0.01). Antibiotics were administered *after* the radiograph (rather than vice versa) in significantly more patients with a TXR <4 hours compared to patients with TXR ≥4 hours (89.8% versus 40.7%, odds ratio 12.8, p<0.001).

Outcome	Survivors to discharge (n=397)		p value
	TXR <4hours (n=291)	TXR ≥4hours (n=106)	
Median hospital length of stay (days)	5.75	7.13	**<0.01**
Interquartile range (days)	8.77	12.56	
30-day readmission rate (%)	16.6	15.2	0.754
Chest radiograph before antibiotics (%)	89.5	41.7	**<0.01**
TFA <4hours (%)	69.2	30.1	**<0.01**

TXR: time from admission to first chest radiograph; TFA: time to first antibiotic dose.

Table 11.3. Comparison of outcome according to time to first chest radiograph.

No statistically significant association was observed between 30-day mortality and TXR or TFA <4 hours, although there was a trend towards a lower mortality in both groups (table 11.4). Of patients who had low severity CAP (CURB-65 of 0 or 1), 4 (7.5%) deaths at 30 days were noted in those with TXR ≥4 hours compared to no deaths in those who had both a TXR <4 hours ($p<0.01$). Having a chest radiograph before antibiotic administration was not associated with a decrease in mortality.

	Total (n=461)	TXR <4hours (n=333)	TXR ≥4hours (n=128)	TFA <4hours (n=245)	TFA ≥4hours (n=181)
CURB65 0-1 Mortality (%)	4/180 (2.2)	0/127 (0)*	4/53 (7.5)*	0/91 (0)†	4/76 (5.3)†
CURB65 2 Mortality (%)	24/151 (15.9)	15/107 (14.0)	9/44 (20.5)	9/74 (12.2)	12/68 (17.6)
CURB65 3-5 Mortality (%)	35/130 (26.9)	26/99 (26.3)	9/31 (29.0)	20/80 (25.0)	11/37 (29.7)
Total (%)	63/461 (13.7)	41/333 (12.3)	22/128 (17.1)	29/245 (11.8)	27/181 (14.9)

TXR: time from admission to first chest radiograph; TFA: time to first antibiotic delivery. *,†: $p<0.05$, Fisher's exact test.

Table 11.4. Association of mortality with time to chest radiograph or antibiotic administration, stratified by pneumonia severity.

Discussion

The main finding of this study is that a TXR of less than four hours is associated with a shorter hospital LOS. A decrease in median LOS of just over a day may seem like a modest figure, but it has been shown that with a condition as common as CAP, small changes in LOS can result in substantial cost benefits nationally.[16] Furthermore, significantly more patients received antibiotics *after* chest radiography if the chest radiograph was performed within four hours of admission rather than beyond four hours.

The link between early chest radiography and length of stay

This is the first paper to our knowledge to demonstrate that TXR is associated with benefits in terms of clinical outcome. There are several potential explanations for this finding. There may be clinical factors that we have not controlled for which are affecting both TXR and LOS, such as higher clinical complexity of patients producing delays in care processes including subsequent hospital discharge. However, no differences were observed between the early and late TXR groups in terms of the presence of co-morbidities, performance status and disease severity. An alternative explanation is that an early chest radiograph is a surrogate marker of quality of care in the management of CAP. This complements a previous study which suggested that prompt diagnostic assessment as measured by early oxygenation assessment for CAP was associated with better quality of care and consequently improved outcomes.[311]

Benefits of advocating early chest radiograph rather than early antibiotics

This study supports the findings from previous reports that an early antibiotic strategy for CAP is associated with a shorter hospital LOS.[324] Unfortunately, an emphasis on early antibiotic delivery as a quality measure has been shown to encourage admitting teams to over-diagnose CAP and over-prescribe antibiotics.[329, 330] Such inappropriate administration of broad spectrum antibiotics can cause considerable harm, including the promotion of antibiotic resistance and antibiotic-associated complications, such as

Clostridium difficile infection. There is also a significant group of patients presenting to acute services for who the diagnosis of CAP is equivocal when based on clinical features and basic investigations alone.[322]

On the other hand, a management strategy based on early radiological diagnosis for patients admitted with suspected CAP *followed by* antibiotic treatment not only provides greater diagnostic accuracy and promotes a more informed approach to patient management, but also potentially enables a reduction in antibiotic use where the diagnosis of CAP is not substantiated by chest radiography. This approach would improve antibiotic stewardship and limit the inappropriate use of antibiotics.

Factors influencing time to chest radiograph

There are several factors which might influence how rapidly a patient arriving to hospital receives a chest radiograph. A previous study demonstrated a shorter TFA in patients with severe pneumonia as defined by a high pneumonia severity index score.[325] The current study replicated this finding and also revealed a similar effect on TXR. Resource issues such as nurse and doctor availability, and number and timing of patient admissions may also have an impact on TXR. These issues are harder to assess quantitatively. In this study, no difference in the proportion of patients with a short TXR was noted in those admitted “out of hours” compared with those admitted during working hours (9am to 5pm). This is an incomplete surrogate measure of resource issues and further research is warranted in this area.

Study criticisms

The main criticism of this study is the possibility that the differences found in LOS were confounded by other undocumented variables. We have compared early and late TXR groups by several clinical variables including presenting symptoms, CAP severity, functional status and co-morbidity. The only differences found between the groups were a higher proportion of patients with TXR ≥4 hours receiving antibiotics in the community prior to admission, and a borderline lower frequency of breathlessness

as a presenting symptom. Nevertheless, there remains a possibility of incomplete adjustment for disease severity and/or other clinical factors.

Length of stay is a less robust end point compared with mortality and may be confounded by other process of care factors such as delays in organising social care. The exclusion of patients admitted from nursing homes who generally have greater social needs would have reduced the impact of social care factors. Nevertheless, residual confounding cannot be completely discounted.

As indicated by the sample size calculations, the study cohort was insufficiently large to demonstrate a mortality benefit. Although a trend towards a lower mortality was demonstrated for patients with TXR <4 hours, a much larger dataset would be required in order to detect a statistically significant difference, if present.

Conclusion

A chest radiograph performed within four hours of hospital admission for CAP is significantly associated with a shorter hospital LOS and antibiotic administration *after* chest radiography. It may represent a useful process of care marker in the management of community-acquired pneumonia.

Chapter 12: The value of early review by a chest physician on outcome

"…for ten to fifteen patients out of every hundred, the balance could be tipped either towards recovery or towards death by the employment or not of correct treatment and careful nursing."

"Diseases of the Chest", Dr Robert Coope (1944)

Introduction

Patients with non-severe CAP have a low mortality and therefore may be suitable to be managed at home, or after a short inpatient stay.[266, 285] Only a small proportion of CAP is managed in hospital,[7] but this fraction accounts for the majority of the financial burden from this disease.[13, 14] Outpatient management of non-severe CAP is as safe and effective as hospitalisation, and these patients often prefer outpatient to inpatient treatment.[339-342]

The aim of this study was to investigate whether patients admitted to hospital with non-severe CAP and managed by respiratory physicians have a shorter LOS compared with patients seen by their general medical colleagues. Our hypothesis was that, compared to general physicians, respiratory specialists are more aware of severity assessment guidelines and have wider experience in managing CAP, and are therefore better able to expedite discharge decisions for patients with non-severe CAP.

Methods

Study population

This study was not part of the cohort study as described in chapter 4, and was conducted solely at Nottingham City Hospital, a busy UK teaching hospital of 1,000 beds. Admissions with CAP to the medical emergency short stay unit (ESSU) over the four-year period 2004 to 2007 were retrospectively examined. Admissions are streamed to this unit by a nurse triage system that selects patients who are felt to be suitable for early discharge following a short admission. Patients with either a primary or secondary international classification of diseases version 10 (ICD-10) admission code of pneumonia or lower respiratory tract infection (LRTI) were identified from computer records. Patients admitted over the same time period with an admission code of cellulitis were identified as a control group. The ICD-10 codes used for data retrieval were as follows: J18.0 (“bronchopneumonia”), J18.1 (“lobar pneumonia”) J18.9 (“pneumonia, unspecified”), J22 (“unspecified acute lower respiratory tract

infection"), L03.0 ("cellulitis of finger and toe"), L03.1 ("cellulitis of other parts of limb") L03.2 ("cellulitis of face"), L03.3 ("cellulitis of trunk"), and L03.9 ("cellulitis, unspecified"). Information recorded included name, hospital number, date and time of admission, date and time of discharge, readmission within 30 days with the same condition, and all other ICD-10 clinical codes relating to the index admission. All discharge summaries and reports of chest radiographs made by the duty radiologist at the time were available and examined for the CAP cohort. Subjects defined as having CAP included all those with radiological evidence for CAP (as reported by the duty radiologist at the time) and who were managed as CAP during their admission.

Patients from both cohorts were excluded if CAP or cellulitis were not the main reasons for admission, if they were seen by a non-consultant grade doctor and subsequently discharged without having seen a consultant physician, or if the patient had an active haematological malignancy requiring admission to a haematology ward. Additionally, patients from the CAP cohort were excluded if they had empyema, hospital-acquired pneumonia, post-obstructive pneumonia due to lung cancer, or mesothelioma. Hospital-acquired pneumonia was defined as presentation to hospital within ten days of a previous admission. In order to confirm that the majority of patients seen on ESSU following nurse triage had non-severe CAP, a random sample of 210 sets of notes representing 50% of the CAP cohort was examined in more detail. The severity of disease as measured by CURB-65 and modified early warning score (MEWS) was ascertained for these patients.[285, 406] This notes review was also used to validate whether individual patient data had been allocated and analysed correctly according to the criteria described below.

Data analysis

Consultant-led post-take ward rounds (PTWR) took place on a daily basis, starting at 9am. Each day the round would be led by a different consultant, determined by a weekly rota, who would review each patient admitted during the preceding 24 hours. The consultant rotas for the study period were used to establish whether the lead

physician on any particular day was a respiratory specialist or from another medical speciality. Patients were divided as to whether they saw a consultant respiratory physician (group A), a consultant physician of another speciality (group B), or were first seen by a consultant physician of any speciality on a Saturday or Sunday PTWR (group C). Patients in group C were considered separately as many of the discharge and diagnostic services at weekends are reduced, potentially prolonging LOS. The primary outcome measure was LOS. Secondary outcome measures were the proportion of patients that were discharged in the 24 hours following first consultant physician review, the proportion of patients that were readmitted within 30 days of the index admission, and 30 day mortality.

Statistical analysis

Microsoft Excel 2003 (© Microsoft Corporation 1985-2003) was used to store and manage the data. Statistical analysis was performed using SPSS version 16.0 for windows (© SPSS Inc. 1989-2007). A Kruskal-Wallis test was used to compare non-parametric data on LOS, with the null hypothesis being that early review by a respiratory physician results in no difference in LOS compared with review by a non-respiratory specialist or on a Saturday or Sunday. Pearson's χ^2 test was used to compare proportions of patients discharged within 24 hours of their first PTWR. A p value of <0.05 was taken as statistically significant.

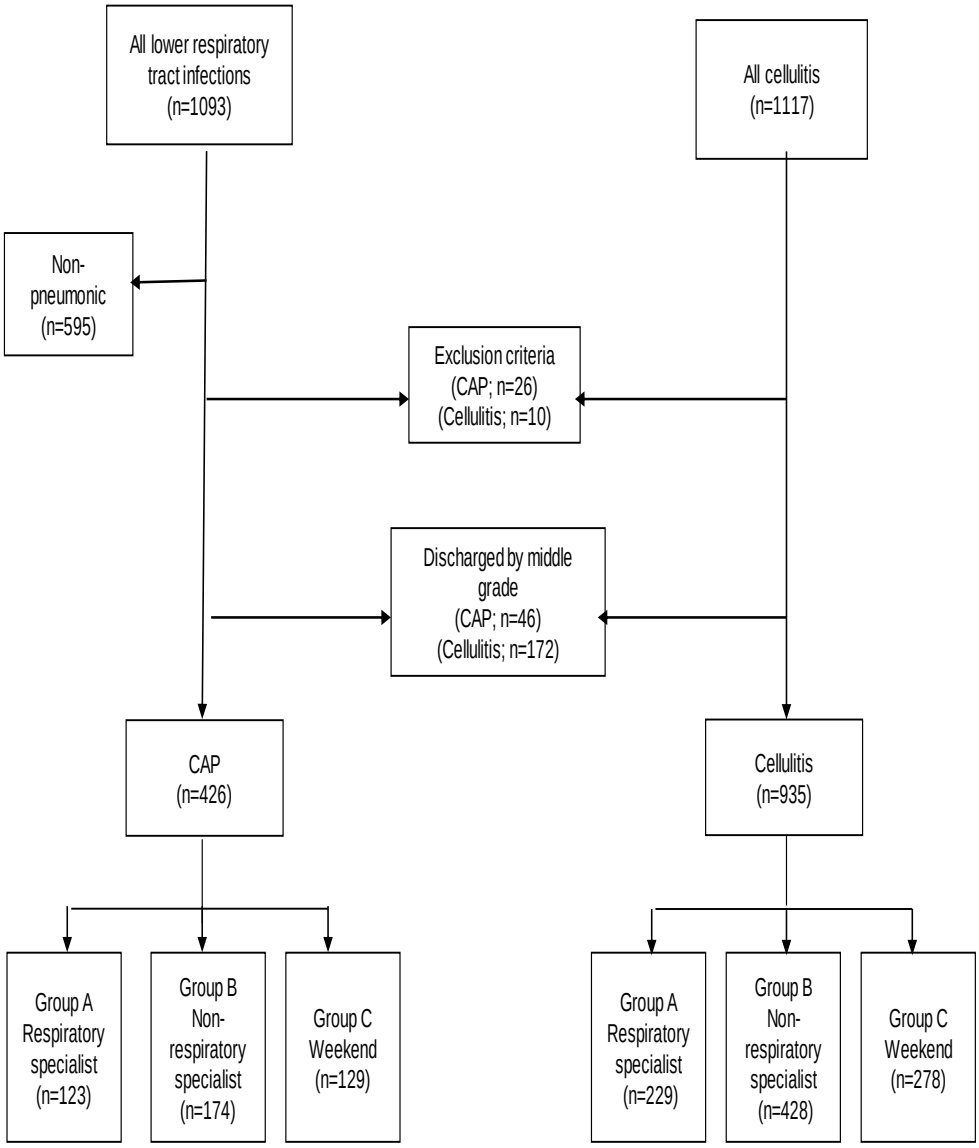
Results

Patient characteristics

1093 patients admitted to ESSU were included in the CAP cohort and 1117 in the cellulitis cohort. The following patients were excluded from the analysis: a) 595 patients in the CAP cohort who were not treated for CAP or did not have acute pulmonary infiltrates on chest radiography; b) 46 patients in the CAP cohort and 172 patients in the cellulitis cohort who were discharged without seeing a consultant; and c) 26 patients in the CAP cohort and 10 patients in the cellulitis cohort who met other exclusion criteria. These data are summarised in figure 12.1 and table 12.1.

Reason	N
No radiographic abnormality consistent with infection	595
Post-obstructive pneumonia	6
Haematology admission	7
Hospital-acquired pneumonia	5
Mesothelioma	3
Empyema	5

Table 12.1. Exclusions from the CAP cohort (n=1093) and their reason



Group A: first seen by a respiratory physician; group B: first seen by a non-respiratory physician; group C: seen on a weekend post-take ward round.

Figure 12.1. Flow diagram illustrating the distribution of patients included in the study.

Patient characteristics are described in table 12.2. From the random selection of 210 (50%) admissions in the CAP cohort examined to establish whether patients had mostly non-severe CAP, 183 (87.1%) had a CURB-65 score of 0 or 1, 18 (8.6%) had a score of 2, and nine (4.3%) had a score of 3 or more. 178 (84.8%) had a MEWS score of less than 5. The 30 day mortality within the CAP cohort after exclusions was 5.2%. These data suggest that the study cohort did comprise mainly of patients with non-severe CAP.

Characteristic	Respiratory Group A	Non-specialist Group B	Weekend Group C
CAP cohort	**n=123**	**n=174**	**n=129**
Mean age (years)	52.6	52.1	53.1
Male (%)	56 (49)	86 (49)	57 (44)
Mean no. of co-morbid illnesses	2.9	3.2	3.4
%CURB65 0-1 (based on 50% sample)	88.2	87.1	86.4
Cellulitis cohort	**n=229**	**n=428**	**n=278**
Mean age (years)	54.0	56.9	56.2
Male (%)	141 (62)	243 (57)	158 (57)
Mean no. of co-morbid illnesses	3.2	3.1	3.2

Group A: first seen by a respiratory physician; group B: first seen by a non-respiratory physician; group C: seen on a post-take ward round on a Saturday or Sunday.

Table 12.2. Characteristics of study population.

No statistically significant difference with regards to age, sex, or co-morbidity was found between the groups A, B, and C in both cohorts. For the patients in whom severity scores were calculated, 88.2%, 87.1% and 86.4% of patients in groups A, B and C respectively had a CURB-65 score of 0 or 1; a similar proportion of scores were calculated for each of the 3 groups. Twenty four (11%) of patients within the random selection examined in more detail were found to have been misallocated to groups A and B based on computer records, with 11 patients incorrectly allocated to group A and 13 patients incorrectly allocated to group B. The results presented below relate to data analysed following the reallocation of these patients to the correct groups.

Length of stay

These results are summarised in table 12.3. Median LOS within the CAP cohort was significantly shorter in group A compared with group B (1.74 days vs. 3.03 days; $p<0.01$). In the cellulitis cohort, there was no statistically significant difference between median LOS (group A: 2.86 days vs. group B: 2.61 days; $p=0.21$). Median LOS for admissions at the weekend (group C) was 2.70 days for the CAP cohort and 2.80 days for the cellulitis cohort.

Characteristic	Respiratory Group A	Non-specialist Group B	Weekend Group C
CAP cohort	**n=123**	**n=174**	**n=129**
Median LOS in days	1.74*	3.03*	2.70*
IQR	0.97-4.09	1.12-6.23	1.31-5.38
% Discharged within 24 hours	43.1	31.9	22.5
Readmissions within 30 days (%)	5 (4.1)	7 (4.0)	6 (4.7)
Cellulitis cohort	**n=229**	**n=428**	**n=278**
Median LOS in days	2.86	2.61	2.82
IQR	1.32-6.16	1.11-6.07	1.20-5.99
% Discharged within 24 hours	24.9	31.5	26.3
Readmissions within 30 days (%)	8 (3.5)	15 (3.5)	18** (6.5)

LOS: length of hospital stay; group A: first seen by a respiratory physician; group B: first seen by a non-respiratory physician; group C: seen on a Saturday or Sunday post-take ward round. *:$p<0.01$ Kruskal-Wallis test. **:$p<0.05$ χ^2 test. IQR: interquartile range.

Table 12.3. Comparison of length of stay, proportion of patients discharged within 24 hours of first PTWR, and readmissions within 30 days with nature of first consultant review.

Within the CAP cohort, more patients in group A (43.1%) were discharged within 24 hours of the first PTWR compared with group B (31.9%), but the difference did not achieve significance at the 5% level (p=0.18). Overall, there were significantly more patients discharged within 24 hours following weekday PTWRs (groups A and B) compared with Saturday and Sunday PTWRs (group C; 38.4% vs. 22.5%, p=0.001). In the cellulitis cohort the proportions discharged within 24 hours were 24.9%, 31.5%, and 26.3% for groups A, B and C respectively. Readmission rates were similar within both cohorts between the groups A and B. However, there was a statistically significant increase in the readmission rate for cellulitis in those first admitted at a weekend compared to those admitted on a weekday (6.5% vs. 3.5%; p=0.04).

Discussion

This is the first study that compares the front-door consultant-led management of non-severe CAP between respiratory and non-respiratory physicians. The principal finding was that early review by a respiratory physician significantly reduces LOS without affecting readmissions rate. In keeping with the decrease in LOS, there were a higher percentage of discharges within 24 hours of consultant review in group A compared with group B, although this was not statistically significant.

There are several possible explanations for these findings. A previous study has compared the chance of CAP treatment failure when managed by respiratory versus non-respiratory specialists.[407] Guideline adherence was lower and treatment failure higher if the patient was managed by a non-respiratory specialist. The study concluded that this difference was due to the better access respiratory specialists had to CAP guidelines, facilitating prompt decision making. The data also suggested that guideline adherence by respiratory specialists promoted a more guideline-based management by non-specialists, implying that respiratory specialists have a training role in the management of CAP. An intensive period of CAP guideline education has been shown to significantly reduce LOS and decrease all-cause 30 day mortality in a hospital setting,=[408]=[408] suggesting that familiarity with CAP guidelines can have an

impact on LOS. The CURB-65 score is the CAP severity assessment tool used within our hospital, and is well known to both junior and senior members of the acute medical team, regardless of their speciality. Nevertheless respiratory physicians may have greater familiarity with these guidelines and their implications. In addition, their more extensive experience in managing CAP may lead to greater confidence in discharging patients earlier.

Patients admitted with cellulitis were selected as a control group because this is a common general medical condition that has no specific affinity to any medical speciality covered by the admitting general medical consultants at this hospital. No difference in the management of cellulitis, and therefore in LOS, was expected. The LOS in this control group was similar between respiratory and non-respiratory physicians, suggesting that the difference in LOS in the CAP cohort was not because respiratory physicians generally adopt a more aggressive discharge policy compared with non-respiratory physicians, nor because of more efficient processes of care occurring on the days when respiratory physicians led the PTWR.

Hospitals in the UK and Europe are increasingly incorporating medical emergency short stay units into their models of acute care. Although there is no recognised standard configuration for these units, the most recent UK recommendations suggest that it be a unit located in close proximity to an acute medical unit, staffed by the same team of doctors, and consisting of beds for patients who should complete their inpatient care without transfer to a specialist medical bed (http://bookshop.rcplondon.ac.uk/contents/pub235-b42eb97d-209b-4ecd-9127-ef95cc21c819.pdf). Our short stay unit conformed to this model of acute care.

Study weaknesses

There are several potential weaknesses with this study. It was a retrospective study, and CAP admissions that were incorrectly coded may have been missed. This was guarded against by reviewing not just the records of patients with a primary and

secondary admission code of CAP, but also all other patients with LRTI. A substantial proportion of these subsequently turned out to have had CAP when the discharge summaries and chest radiographs were examined. However, there may have been other patients with CAP who were incorrectly coded in other ways.

The patients with CAP seen by respiratory physicians may have had less severe disease compared with those seen by non-respiratory physicians. However, CURB-65 scores were similar between the groups in the 50% of the CAP cohort for whom severity scores were calculated. In addition, there were no statistically significant differences between the two groups in terms of age or number of co-morbid illnesses. Practically, there was no reason to expect a systemic difference in disease severity between the two groups either.

Within the random patient sample whose notes were examined in greater detail, 24 (11%) patients had been assigned to the incorrect patient group. This discrepancy was likely due to late changes in the consultant rota that were not officially documented. It is unknown whether patients in the remaining 50% of the cohort had a similar misallocation rate. The observed differences between groups A and B were greater when these data were analysed following reallocation of these 24 patients compared to analysis without reallocation. If a similar misallocation rate were assumed in the remaining 50% of the CAP cohort then the differences would be expected to be further exaggerated and therefore do not detract from the main findings of this study.

Conclusions

Patients with CAP who are not severely ill have a shorter hospital LOS when initially seen by a respiratory compared to a non-respiratory physician. This may have implications for the acute medical service, implying a benefit of early respiratory review of all CAP admissions.

Chapter 13: Closing remarks

“The doctor’s attitude must be, however, not to wait and see, but rather to wait and foresee; for seven days or so he will be playing a game of chess, as it were, and he must try always to be a move ahead of his opponent.”

“Diseases of the Chest”, Dr Robert Coope (1944)

The outcome of community-acquired pneumonia may be improved by focusing on both disease *management* and *prevention*, primarily through vaccination. Adequate vaccination strategies rely on surveillance of the prevalent pneumococcal serotypes in order to ensure that the current vaccine incorporates the circulating serotypes. Studies contained within this thesis have shown that the serotypes prevalent in pneumococcal disease may be changing. Furthermore, as each serotype is associated with specific associations with clinical disease, this change may be associated with significant changes in the pattern of CAP seen by admitting clinical teams. A driver of this change may be vaccination of infants against the formerly more prevalent serotypes, promoting "herd immunity" to these serotypes in a population group from where the majority of disease is thought to originate. This strengthens the hypothesis that a major mode of pneumococcal transmission is from colonised children.

This has several implications. Firstly, the fact that a change in the spectrum of adult CAP can be affected by vaccinating a separate population group is potentially an unforeseen advantage of infant immunisation. Additionally, future vaccine development may be informed by monitoring changes in the prevalent serotypes in adult disease. The successor to PCV-7 (the 13-valent vaccine PCV-13) contains many of the serotypes identified in these studies, with the notable exception of serotype 8. The structure of the conjugate vaccine prevents inclusion of more than around fifteen serotypes; therefore progressive addition of novel emerging serotypes will not be possible. However, a strategy where the leading serotypes are included in a vaccine that changes annually may be of benefit. Thirdly, different serotypes seem to have distinct clinical associations. Therefore, any change to the circulating serotypes may dramatically change the nature of CAP seen by admitting units; rather than preventing disease, selective serotype vaccination may just be promoting serotypes that cause "unusual" pneumococcal CAP, which may paradoxically increase the morbidity of the population due to pneumococcal CAP. Future work in this area will be required to continue to monitor the changes in both pneumococcal

serotypes and the clinical spectrum of pneumococcal disease following the introduction of PCV-13. Further years' data are also desirable to show that the differences between years one and two are not purely attributable to natural annual variation in serotype circulation. A direct link between pneumococcal colonisation in children and CAP in adults may only be proved by extending this surveillance to near real-time nasopharyngeal sampling of child and infant contacts of adults with CAP, which may be a productive area of future work.

Studies contained within this thesis have identified five major areas where the CAP care process may be improved, or better identify patients at increased risk of adverse outcome. Assessment of both hypoxaemia at admission and poor baseline performance status may help to identify sub-groups of patients who are at increased risk of death, and may therefore benefit from higher levels of clinical concern. The role of oxygenation and functional status assessment seems to be in parallel to existing severity scores rather than as a replacement. They may identify groups of patients at increased risk of adverse outcome despite being classified as low or moderate severity by traditional severity scores. Calculation of a simple symptom score may inform clinical progress on a daily basis, and identify patients at risk of clinical failure and adverse outcome. Finally, early diagnosis (by means of early chest radiography) and early review by a respiratory specialist have been shown to reduce length of hospital stay without significantly increasing re-admission rate. However, each of these studies is observational in nature. A more robust way of identifying beneficial interventions would be to enrol patients in a randomised controlled trial; unfortunately, such trials would have to consist of large numbers of participants to attain adequate statistical power.

The proposed interventions are all either low cost or easy bedside assessments, and should be relatively easy for any hospital to introduce. A step further would be to triage adults with CAP early in the admission process to a specialist respiratory (or ideally, respiratory infection) receiving area, where these interventions might be

delivered by specialist nursing and medical staff. Not only would this allow for these interventions to be rigorously incorporated into patient care, but it would also facilitate audit of their potential benefits. Improvements in length of hospital stay could be an attractive incentive to UK hospital trusts where pressures in acute medical beds are a continuing problem.

Appendix 1: Standardised operating procedure for the Bio-Plex assay

TITLE	Pneumococcal Serotype Specific Bio-Plex assay – Clinical Sample Method.

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SUMMARY

This document describes the procedure and safety aspects for performing a serotype specific pneumococcal Bio-Plex assay directly on clinical specimens. This includes sample preparation, the test procedure, and how to use the Bio-Plex Instrument.

SAFETY

Good Laboratory Practise. Wear gloves and safety glasses throughout the procedure.

Refer to COSHH assessments: - Biological and Chemical.

RB0003 – Detection of bacterial antigens/DNA in urine samples

RB0005 – Handling of lower respiratory tract (LRT) specimens

RB0006 - Use of animal sera/material in diagnostic/reference tests.

RB0007 – Detection of bacteria, antigens or DNA in sterile site specimens

RC0041 – Use of QIAamp DNA mini kit (covers Proteinase K)

RC0053 - Luminex 100 instrument run reagents.

RC0089 - Pneumococcal typing

Risk Assessments:

RG0001 - Use of centrifuges

RG0018 – Use of Containment level 3 (CL3) Room
RG0036 - Millipore vacuum manifold and moisture trap
RG0038 - Plate shaker
RG0039 - Grant heating block
RG0044 - Luminex 100 multi-analyte array system
RG0045 - Ultrasonic bath
RG0050 – Use of class 1 safety cabinet
RG0053 – Vacusafe system
RSIL safety manual

INTRODUCTION

Luminex xMAP microsphere technology (Luminex Corp. USA) has the potential to greatly decrease the complexity and run time of immunoassay assays as multiplex assays can be performed in a in a matter of minutes from a small sample volume. The technology is based on the use of microscopic polystyrene beads labelled with differing amounts of red and infrared dyes, which enables the differentiation of up to 100 different beads by the Luminex or Bio-Plex instrument. Each different bead type can be conjugated to a different antibody (or antigen) and the instrument detects a positive result on any particular bead by the presence of a fluorescent reporter antibody.

NB: The Luminex 100 instrument in RSIL is now referred to as a Bio-Plex instrument as it has been upgraded by installation of Bio-Plex manager 4.0 software, (Bio-Rad). The instrument consists of the Bio-Plex analyser, the XYP platform and Luminex SD unit. The Bio-Plex instrument uses a precision fluidics system to pass the sample though two laser detectors one bead at a time. The XYP platform enables higher throughput and automatic running of up to 96 samples in a microtitre plate format.

This protocol describes the procedure for preparation samples for testing in serotype specific immunoassays, as well as the general procedures for running a serotype specific pneumococcal antigen assay using Bio-Plex technology.

MATERIALS

Preparation of clinical samples for use in the serotype specific Pneumococcal Bio-Plex assay (materials needed varies depending on sample type).

- R+D Bio-Plex set-up worksheet (Excel spreadsheet file)
- Pipettes and tips
- Sterile PBS - HPA Media Services
- Sterile dH_2O - HPA Media Services
- 1.5ml Screw-cap tubes
- 1M HEPES
- Proteinase K 600AU/ml (Qiagen)
- Sputasol (Oxoid)
- Heating block set at 100°C
- Heating block set at 56°C
- Laboratory timer
- Eppendorf 5415D or similar bench top centrifuge capable of 16,000g
- Sarstedt or similar 0.45µm syringe filter
- 3ml syringe with luerlok fitting

Pneumococcal serotype-specific multiplex assay

- Bio-plex set-up worksheet (Excel spreadsheet file)
- Sterile PBS - HPA Media Services
- PBST (250µl Tween in 500ml PBS), Tween – BDH 437082Q
- Multichannel Pipettes – 0.5-200µl, 50-300µl, and sterile tips
- Micropipettes and sterile tips
- Stepper pipettes – 20-300µl and 200-2000µl and tips
- Bio-Plex instrument including XYP platform and sheath delivery system.
- Sheath fluid (Luminex or Bio-Rad)
- Calibration Bead kit - Bio-Rad Cat. No: 171-203060

- Pre-prepared Multibead aliquots (1/2 plate) of Pneumococcal serotype-specific monoclonal antibody coupled Luminex xMAP beads (see Appendix 2 for antibodies coupled to beads): Regions
    - 4 (coupled with SSI anti-c polysaccharide monoclonal antibody),
    - 13 (coupled with serotype 6B specific Wyeth Monoclonal antibody),
    - 24 (coupled with serotype 7F/A),
    - 28 (serotype 5),
    - 29 (serotype 19A),
    - 34 (serotype 14),
    - 38 (serogroup 18),
    - 41 (serotype 8)
    - 46 (serotype 9V),
    - 54 (serotype 23),
    - 60 (serotype 19F),
    - 66 (serotype 6A),
    - 73 (serotype 1),
    - 17 (serotype 3)
    - 77 (serotype 4).
- Millipore multiscreen MSBVN1B (opaque) 1.2µm plates
- Dedicated Millipore vacuum manifold
- Vacusafe system
- Vortex mixer
- Pierce Starting Blocking Buffer - Cat No: 37543
- Ultrasonic bath
- Reagent reservoirs
- Ready for use aliquot/s (1/2 plate) containing a mixture of desalted and filtered Statens Serum Institut (SSI) polyclonal serum for serogroups 1, 3, 5, 7, 9, 14, 23 and C-Polysaccharide, and Melon gel Purified IgG from SSI polyclonal serum for serogroups, 4, 6, 8, 18, and 19 at 20µg/ml protein concentration. See 2 for details of antibodies)

- Polyclonal - anti-rabbit RPE conjugate (goat) - (Pierce pharmaceuticals Cat No: 31864)
- Aluminium foil backed grooved lids
- Bio-Plex set-up worksheet (Excel spreadsheet file)
- Aluminium foil
- Absorbent paper e.g. blue roll
- Bio-Rad validation Kit - Cat No: 171-203001

PROCEDURE

- Wear gloves and safety glasses for all procedures.
- NB: The high level of sensitivity of the Bio-Plex pneumococcal antigen detection assay is comparable to that of a PCR assay. Unfortunately this means that the assay is vulnerable to contamination events (i.e. pneumococcal polysaccharide may enter a reagent and cause high background or unacceptable levels of fluorescence in Bio-Plex assays). Therefore it is necessary to apply a semi-clean room approach to the preparation of assay reagents and running of assays. To avoid contamination problems happening, the assay should be regarded as if it were a PCR and the necessary precautions taken.
- Measures to avoid contamination in pneumococcal Bio-Plex assay reagent preparation and runs are detailed in Appendix 1.

Preparation of Bio-Plex Assay Worksheet.

- For the pneumococcal serotyping Bio-Plex assay, first set up the 96 well plate format using the Excel worksheet template found on Z:drive (Clinical sample worksheet). Set up the control wells and add the sample reference numbers (these can be scanned in) to sequential wells. The number of columns/wells used is then entered into the calculation boxes of the sheet to indicate the number of bead and polyclonal aliquots needed (made up in half plate aliquots), and the amount of Pierce Blocking Buffer to dilute them in. It also details the volume of

anti-rabbit RPE conjugate needed, and the amount of Pierce Blocking Buffer to dilute it in.

- Save the assay template, then print the worksheet out and use it for reference in the following procedures. Wear gloves and eye protection for all following laboratory procedures.

Urine sample preparation.

- Add 1:40 v/v 1M HEPES buffer to the urine to give a final concentration of 25mM HEPES. This buffer neutralises the pH of the urine.
- Centrifuge the urine aliquot at 14000g for 10 minutes to pellet debris.
- If the sample is particularly viscous or contains a lot of sediment, remove the supernatant carefully without disturbing the pellet and filter using a 0.45µM syringe filter (if filtering is necessary a larger volume of urine will be needed to ensure enough volume remains for testing).
- Test 100µl prepared urine per well in the Bio-Plex assay.

CSF sample preparation

- Centrifuge the sample at 16,000g for 2 minutes.
- Dilute CSF sample 1:3 in sterile PBS (e.g. 70ul sample in 140ul PBS to provide 2x sample wells)
- Vortex diluted sample briefly and pulse centrifuge to remove drops from lid.
- Test 100µl of diluted CSF per well in the Bio-Plex assay.
- If <70µl but >20µl CSF is present, dilute entire volume 1:3 in PBS, test half the diluted volume in two wells on plate. E.G if approx 30µl CSF present dilute in 60µl PBS and test 45µl in each well of the plate.
- If <20 ul sample remains (or even if sample tube appears empty), add 40ul PBS directly to the sample tube, vortex, pulse centrifuge and test entire volume in one well of the assay plate. Mark original tube as “washout” to indicate that the sample has been washed out with PBS. It is sometimes possible to get a positive result

just from the residue remaining in a CSF sample tube. Mark any test volume or duplicate number changes on the worksheet.

- If the test is negative repeat test at 1:2 dilution if sufficient sample remains.

Empyema/pleural fluid sample preparation

- Empyema and pleural fluids from children <16 years may be tested in the Bio-Plex assay at Cat 2 provided the sample is be initially processed in CL3 for steps 4.4.1 to 4.4.10 all pipetting steps at CL3 are performed in a class 1 safety cabinet.
- If sample can easily be aspirated using a pipette, skip to step 4.4.5.
- If the sample is very viscous and cannot be pipetted, add an equal volume of freshly prepared Sputasol.
- Incubate for 10-60 minutes at 37°C until sample has liquefied.
- Remove 400µl liquefied sample (1:2 dilution) and place in screwcap tube, add 20µl proteinase K (Qiagen) - skip to step 4.4.6.
- Aliquot 200µl pleural/empyema fluid sample into a screw cap tube and add 10µl proteinase K
- Incubate samples with Proteinase K for 10 minutes at 56°C on a heat block.
- Centrifuge samples for 2 minutes at 16,000g
- Dilute an aliquot of the digested fluid sample in PBS to achieve a final 1:5 dilution (100ul in 400µl PBS for samples without sputasol and 200ul in 300 ul PBS for samples with sputasol).
- Heat the diluted sample for no less than 10 minutes at 100°C on a heating block to inactivate potential cat 3 organisms .
- Centrifuge samples for 5 minutes at 16,000g
- Test 100ul per well of diluted heat-treated sample, if negative repeat test using 1:2 dilution of treated fluid sample.

Pneumococcal serotype-specific multiplex assay

- Set up the Excel worksheet to define the wells in which the samples and controls are going to be placed and also calculate the amount of reagents needed. Print out the work sheet and the batch number record which is used to keep a record of the batch numbers of reagents used in the assay.
- Pre-wet the filter of the Millipore MSBVN1B plate by adding 125µl PBS and pulling it though the wells using the Millipore vacuum manifold, allow the liquid to flow through the manifold and into the liquid trap. Blot the back of the plate dry using absorbent paper e.g. blue roll. Cover any unused wells on the filterplate with adhesive film,
- Add 100µl (or lower volume if small volume CSF sample) of the diluted sample/control to the appropriate wells of the plate.
- Vortex the aliquot of prepared multiplex bead mixture for 30 seconds and add 25µl to each well of the sample plate. Cover the plate with a foil backed plate lid.
- Incubate the plate overnight (at least 16 hours) on a plate shaker at room temperature.
- Refer to the printed Bio-Plex worksheet to find the appropriate dilution for the polyclonal antibody mixture. Each desalted/filtered polyclonal is at 1/21000 final dilution (1/500 of the 1/42 solution), and the purified polyclonal IgG's are used at 1µg/ml final concentration. Dilute the polyclonal antibody mixture in Pierce Starting block buffer.
- Remove plate from the shaker and take off lid.
- Draw the fluid through the plate using the vacuum manifold with a maximum of 10 inch Hg. vacuum. Blot plate bottom on paper towel.
- Occasionally samples may block the wells of the filter plate. In this case it is sometimes possible to carefully clean the underside of the blocked well with a small piece of blue roll and 70% meths and the sample will flow through. If the sample does not flow through, try cleaning again. As a last resort transfer the sample to an unused well on the plate. If no wells are available re-test the sample

after treatment with proteinase K as this should removes the debris which can block the wells.

- Add 200μl PBST to each well with repetitive pipetting to agitate the beads.
- Draw the liquid through the plate with vacuum allowing the wash liquid to flow through to the trap.
- Repeat wash three times without repetitive pipetting.
- Blot the plate on paper towel and add 100μl per well of the polyclonal antibody mixture prepared as stated above.
- Clean the inside of the plate lid with 70% meths.
- Cover the plate as before and shake at room temperature for 1 hour.
- Meanwhile switch on the Bio-Plex instrument, perform the start up, and warm up procedure as stated in SOP R6558. It is necessary to calibrate the instrument before the first run of the day so this should be done as stated in the above SOP using the High calibration target value.
- Make up polyclonal goat-anti-rabbit RPE conjugate solution as stated on Bio-Plex worksheet (1:200 dilution) in Starting block buffer. Cover the tube with foil to avoid photo-bleaching of the dye.
- Wash the beads
- Blot the bottom of the plate dry and add 100μl per well of diluted RPE conjugate. Cover the plate and incubate for 30 minutes shaking at room temperature.
- Meanwhile set up the run protocol on the Bio-Plex software. Open the “Clinical sample” protocol and click “select analytes”. Check that the correct bead types are included in the assay.
- Click “Format Plate” and select the wells containing standards, controls and unknown samples. NB: select the negative control wells as controls rather than blanks unless you want the instrument to blank the signal on the negative wells in the results screen. Make sure that the numbering of the samples is in the chronological order that you expect; sometimes the numbering gets disrupted if you click later wells before previous ones, which can cause confusion when the sample names are entered.

- To get automatic test/negative ratios, group the samples and set the appropriate negative control as the reference, make sure member/reference is selected in the dropdown box. Then when the results are presented the software will automatically compare the test sample to the negative control reference as a ratio.
- Click the tabs to enter the standard, control and sample information. Sample information from the Bio-Plex work sheet can be directly copied and pasted into the sample information fields. Make sure that the standards have their concentrations entered.
- Click Run protocol and make sure that the top drop down box is set to count 100 beads per region. The instrument is now prepared for running the protocol.
- Remove the plate from the shaker and wash as stated before.
- Blot the bottom of the plate on blue roll and re-suspend the beads in 125µl PBS by repetitive pipetting. Re-cover the plate and leave on plate shaker until it is to be read, the plate must be shaken for at least 30 seconds prior to reading.
- Click the “Start” button to begin the process and the software will ask you to insert the sample plate. Click “eject/retract plate” and place the plate on the plate holder.
- Click OK to start the run.

INTERPRETATION OF RESULTS

- The result table from the Bio-Plex software can be exported to excel in a variety of formats. The columns exported are customisable from within the Bio-Plex software. Standard curves can be printed of each assay type. Usually only the mFI data and ratio data are exported.
- The results for CSF and clinical samples other than urine are currently being analysed by the use of test to negative ratios where the test count results are divided by the negative control count result for that bead type in order to give a T/N ratio. The worksheet *Z:/Bioplex/Clinical result score sheet* can be used to automatically score results for CSF and pleural fluid specimens. On this sheet T/N ratios of greater than 3 are currently considered to indicate a positive and the worksheet also flags up potential false positive and false negative results based

on the strength of sample signals. However the background signals and obtained in all the serotype assays for a single sample and the C-polysaccharide result should be taken into account when deciding whether a sample is positive for a particular serotype.

- For urine specimens a worksheet has been devised by colleagues at Wyeth vaccines to set the cut-off FI value for each assay based on the results of the standard curves.
- Print outs of the Bio-Plex worksheet set-up template and batch number record MUST be placed with print outs of the raw mFI data and final results of each assay and kept in appropriate files depending on the sample types tested. If samples from more than one study are tested on the same plate then photocopies of the sheets must be made and placed in appropriate files.

DISCARD/DECONTAMINATION PROCEDURES

- Discard the sample plate into the plastic waste for autoclaving. Partially used plates can be re-used provided the unused wells have been covered with adhesive film throughout the procedure.
- Follow the shut-down procedure outlined in R6558 to rinse and decontaminate the Bio-Plex instrument.
- If used for infectious sample assays the waste liquid from the Millipore manifold must be decontaminated. Decant the liquid from the bottle into a designated contaminated liquid waste bottle (appropriately labelled) and once the volume reaches 2L add a chloros tablet, leave for 24 hours prior to discard.
- The Millipore manifold must be thoroughly rinsed through with distilled water. Rinse by filling the bottom of the manifold with water and aspirating using the pump.
- After the water rinse procedure, wipe the manifold and grill with 70% meths solution.
- Occasionally (up to once a week if in regular use) a 10% chloros solution may be used to decontaminate the manifold and vacuum tubing. To do this, wipe the

manifold with 10% Sodium hypochlorite and place a small amount (up to 5ml) onto the bottom manifold tray. Draw the liquid through tubing into the liquid trap using the vacuum and rinse thoroughly with distilled water as above. Discard the liquid from the liquid trap.

QUALITY CONTROL

- Prior to use all new batches of coupled beads are checked using standard curves of known concentrations of purified type specific pneumococcal polysaccharide, to check that the same level of sensitivity is achieved from batch to batch of beads.
- Before inclusion into Bio-Plex assay, all new batches of pre-mixed polyclonal are tested. An aliquot is run in parallel in a routine sample run and the results compared.
- The Bio-Plex instrument is validated using the Bio-Rad validation kit that checks all aspects of the instrument function. This validation is performed every six months, the sheet on each Bio-Plex details when the instrument was last validated. Validation records for each instrument are kept on the Z drive in the folder Z:\Bioplex\BIOPLEX VALIDATION REPORTS.

SUMMARY OF REVISION

Details of revision(s)
Revision of some sample preparation methods. Inclusion of detail for when CSF sample volume small. Inclusion of detail about instrument validation.

Measures to avoid contamination in pneumococcal Bio-Plex assay reagent preparation and runs

The high level of sensitivity of the Bio-Plex pneumococcal antigen detection assay is comparable to that of a PCR assay but unfortunately this means that the assay is vulnerable to contamination events (i.e. pneumococcal polysaccharide may enter a reagent and cause high background or unacceptable levels of fluorescence in Bio-Plex assays). Therefore it will be necessary to apply a semi-clean room approach to the preparation of assay reagents and running of assays. To avoid contamination problems happening, the assay should be regarded as if it were a PCR and the necessary precautions taken.

Bead-coupling

- Perform bead-coupling in 4B36 when no cultures are present in the room
- Wear a fresh lab-coat or a lab-coat that has not been worn to handle pneumococcal cultures. (Borrow a lab coat from APU if it is not possible to use your own).
- Wipe surfaces (including pipettes, centrifuge, vortex, and rotator) with 70% meths prior to starting (as if you were working in the PCR cabinet)
- Do not take stock beads (uncoupled or coupled stocks) into lab containing pneumococcal isolates
- Ensure that pastettes and pipette tips used are sterile

Reagent preparation

- Wearing a clean lab coat make up aliquots of bead mixes, polyclonal mixes, in the laminar flow cabinet outside the MLA room. (This cabinet should never have been used for cultures and will protect the reagents from contamination from the worker!)
- Also make small aliquots of all reagents necessary for the run (eg Pierce starting block buffer) in the laminar flow cabinet.
- Ensure that the stocks of assay plates (e.g. PCR plates and filter plates) pipette tips etc are kept sterile at all times (re-seal plastic bags if necessary).

Assay run

- Wipe the work area and pipettes used with 70% meths
- Ensure that fresh PBS is always used for the assay dilution steps
- Remember to thoroughly clean the assay plate lid prior to use
- Use single use aliquots of Pierce blocking buffer.
- If re-using a filter plate that has been used for a previous run, inspect the plate carefully to check for splashes into the unused wells. If contamination is suspected use a new plate.
- Use fresh PBST for the washing steps.

Serotype assay	Bead coating capture antibody				Secondary antibody		
	Antibody type	Treatment	Clone	Conc per million beads	Antibody type	Treatment	Dilution/ Conc
1	Wyeth MAb	Commercially purified	Pn 26-2	3.2ug	SSI Type 1 antisera	Filtered / desalted	1/21000
3	Wyeth MAb	Wyeth purified	Pn 459-1	3.2ug	SSI Type 3 antisera	Filtered / desalted	1/21000
4	Wyeth MAb	Commercially purified	Pn 31-1	3.2ug	SSI Type 4 antisera	Purified IgG	1ug/ml
5	Wyeth MAb	Commercially purified	Pn 55-1	3.2ug	SSI Type 5 antisera	Filtered / desalted	1/21000
6A	Wyeth MAb	Commercially purified	Pn 10-2.1	3.2ug	SSI group 6 antisera	Purified IgG	1ug/ml
6B	Wyeth MAb	Commercially purified	Pn 36-1	3.2ug	SSI group 6 antisera	Purified IgG	1ug/ml
7F/7A	Wyeth MAb	Commercially purified	Pn 503-1	3.2ug	SSI group 7 antisera	Filtered / desalted	1/21000
8	Wyeth MAB	Wyeth purified	Pn 814-1	3.2ug	SSI type 8 antisera	Purified IgG	1ug/ml
9V	Wyeth MAb	Commercially	Pn 45-	3.2ug	SSI group 9	Filtered /	1/21000
14	Wyeth MAb	Commercially purified	Pn 42-1	3.2ug	SSI type 14 antisera	Filtered / desalted	1/21000
18	Wyeth MAb	Commercially purified	Pn 56-1	3.2ug	SSI group 18 antisera	Purified IgG	1ug/ml
19A	Wyeth MAb	Commercially purified	Pn 177-7	3.6ug	SSI group 19 antisera	Purified IgG	1ug/ml
19F	Wyeth MAb	Commercially purified	Pn 63-1	3.2ug	SSI group 19 antisera	Purified IgG	1ug/ml
23F	Wyeth MAb	Commercially purified	Pn 53-2	3.2ug	SSI group 23 antisera	Filtered / desalted	1/21000
Ccps	SSI MAb	Part fractionated for IgM	HASP-8	3.2ug	SSI c-Ps antisera	Filtered / desalted	1/21000

Table of Antibodies used for serotype-specific antigen detection assay. MAb = Monoclonal antibody; SSI = Statens Serum Institut (Copenhagen).

Appendix 2: The CAP score

CAP score questionnaire

Question	level	coding
1. Are you today (XXth day of the evaluation) bothered by shortness of breath when		
	sitting still	◻ yes ◻ no
	walking around the house/ward	◻ yes ◻ no
	washing/dressing	◻ yes ◻ no
	walking in the street	◻ yes ◻ no
	taking a shower	◻ yes ◻ no
	walking the stairs	◻ yes ◻ no
2. If you were to give a mark on a 1 to 5 scale expressing the severity of your shortness of breath at the moment, which mark would that be?		
	not at all short of breath (1)	◻
	slightly short of breath (2)	◻
	fairly short of breath (3)	◻
	substantially short of breath (4)	◻
	terribly short of breath (5)	◻
3a. Do you cough?		
	no (skip questions 3b, c and d)	◻
	only in the morning, when getting up	◻
	now and then, all through the day	◻
	frequently, all through the day	◻
3b. Do you cough up sputum? (amount of sputum by 24 hrs)		
	no	◻
	less than 2 spoons	◻
	more than 2 spoons	◻
	half a cup or more	◻
3c. Do you cough up the sputum with ease?		
	not bothered by sputum	◻
	with ease	◻
	fairly difficult	◻
	very difficult	◻
3d. What is the color of the sputum?		
	did not pay attention/no sputum	◻
	transparent	◻
	white	◻
	green, yellow or brown	◻
4. When the following statement is correct, please check the leftmost box, the less you agree with the statement, one of the boxes on the right can be ticked off		
I feel fit	yes, that is correct ◻ ◻ ◻ ◻ ◻	no, that is not correct
5. If you were to give a mark on a 1 to 5 scale expressing your general state of health at the moment, which mark would that be?		
	excellent (1)	◻
	good (2)	◻
	fair (3)	◻
	poor (4)	◻
	very poor (5)	◻

*Translated from Dutch.

CAP score calculator:

Item*		Quantification	CAP	Respiratory	Well being
Shortness of breath					
walking the stairs	☐ yes 1				
taking a shower	☐ yes 1				
walking in the street	☐ yes 1				
washing/dressing	☐ yes 1				
walking around the	☐ yes 1				
house/ward	☐ yes 1				
sitting still					
	0	☐ 6			
subtotal (sum)	1	☐ -2			
	2-3	☐ -6	→ _____	→ _____	
	4-6	☐ -8			
Severity of shortness of breath					
not at all short of breath (1)		☐ 7			
slightly short of breath (2)		☐ -2			
fairly short of breath (3)		☐ -8	→ _____	→ _____	
substantially short of breath (4)		☐ -11			
terribly short of breath (5)		☐ -13			
Cough					
No		☐ 9			
only in the morning, when getting up		☐ -6			
now and then, all through the day		☐ -6	→ _____	→ _____	
frequently, all through the day		☐ -12			
Cough up sputum					
None		☐ 7			
less than 2 spoons		☐ -8			
more than 2 spoons		☐ -13	→ _____	→ _____	
half a cup or more		☐ -16			
Cough up sputum with ease					
no sputum		☐ 7			
with ease		☐ -9			
fairly difficult		☐ -10	→ _____	→ _____	
very difficult		☐ -10			
Colour of sputum					
did not pay attention/no sputum		☐ 8			
transparent		☐ -8			
white		☐ -8	→ _____	→ _____	
green, yellow or brown		☐ -14			
Feeling fit					
yes, that is correct		☐ 12			
		☐ 4			
		☐ 0	→ _____		→ _____
		☐ -6			
no, that is not correct		☐ -11			
General state of health					
excellent (1)		☐ 14			
good (2)		☐ 8			
moderate (3)		☐ -1	→ _____		→ _____
poor (4)		☐ -9			
very poor (5)		☐ -15			
Raw total		*(sum)*	_____ (A)	_____ (B)	_____ (C)

SCALE TRANSFORMATION

CAP SCORE	= (A + 99) / 1.69	_____		
RESPIRATORY SCORE	= (B + 73) / 1.17		_____	
WELL BEING CORE	= (C + 26) / 0.52			_____

Appendix 3: The child contact questionnaire.

Questionnaire v 1.3
03/07/2008
Participant number

Affix label here

"A Population based prospective cohort study of pneumococcal pneumonia in adults following the introduction of childhood pneumococcal vaccination in the UK"

QUESTIONNAIRE

Thank you for agreeing to take part in our study. As we explained in the Patient Information Leaflet, we'd like to ask you some questions about your contact with children. This questionnaire should take between 5 and 15 minutes to complete. The interviewer will complete the form with you.

1a. Have you had **close social contact** with children in the past 4 weeks?

Examples of close social contact include: living with children in the same household, cuddling or kissing a child, spending a total of 8 hours or more in the company of a child.

YES ☐ **NO** ☐

If YES, go to question 1b. *If NO, go to question 2.*

1b. Please can you define the number of children you have been in close social contact with over the past 4 weeks, the ages of these children, and your relationship to them.

	Number of children	Ages of children
Child / dependant		
Grandchild		
Other close family member (e.g. nephew / niece)		
Other *		

*If other, please specify:

_____

If the patient has indicated that they have contact with a child, dependant or grandchild, go to question 1c, otherwise go to question 2.

1c. If you are the parent, legal guardian or grandparent please can you tell us more about your children/ grandchildren?

We would like to know their names, ages, whether they attend nursery or day care and whether they have been vaccinated with a pneumococcal vaccine (also known as PCV7, pneumo vaccine, pneumococcal conjugate vaccine).

Child 1

Relationship to child: ……

Name of child:……

Age of child: ……

Received pneumococcal vaccine:……

Attends nursery/ daycare:……..

Child 2

Relationship to child:……..

Name of child:……

Age of child: ……

Received pneumococcal vaccine:……

Attends nursery/ daycare:……..

Child 3

Relationship to child: ……..

Name of child: ……

Age of child: ……

Received pneumococcal vaccine:……

Attends nursery/ daycare:……..

In the case of contact with more than 3 children, continue on supplementary sheets

If the patient is the parent of children named above go to question 1d, if they are the grandparent go to question 1e.

1d. Would you allow us to contact your child's GP/ health records so we can confirm whether they have received pneumococcal vaccine?

YES ☐ **NO** ☐

If yes, arrange for parent/ guardian to sign consent form for access to vaccination history

If no, go directly to question 2

1e. Would you allow us to contact the parent/ legal guardian of your grandchildren so that we can ask them for permission to check your grandchild's GP/ health records to confirm whether they have received pneumococcal vaccine?

YES ☐ **NO** ☐

If yes, ask for the names and contact details of the parent/ legal guardian

If no, go directly to question 2

Child:……
Name of parent/ legal guardian:……..
Contact details:……
……

2a. Do you have a job that involves looking after or teaching children?

YES ☐ **NO** ☐

If yes go to question 2b *If no, thank the patient for their time and participation*

2b. What is your job?

Nursery nurse/ day care assistant ☐
Primary school teacher ☐
Secondary school teacher ☐
Sports instructor ☐
Health professional ☐
Other* ☐
*Please specify
……
…….

2c. In the past 4 weeks, please estimate the number of children you have worked with and the and hours of contact you have had with children through your job

Number of children:……

Hours of contact with children:……..

Thank you for completing the questionnaire and participating in our study

Appendix 4: Ethics and research and development approval letters

Nottingham Research Ethics Committee 1
1 Standard Court
Park Row
Nottingham
NG1 6GN

Telephone: 0115 9123344 ext. 39390
Facsimile: 0115 9123300

09 September 2008

Dr WS Lim
Consultant Physician
Nottingham University Hospitals NHS Trust
David Evans Building
Nottingham City Hospital
Hucknall Road
Nottingham
NG8 2NE

Dear Dr Lim,

Full title of study:	**A Population based prospective cohort study of pneumococcal pneumonia in adults following the introduction of childhood pneumococcal vaccination in the UK**
REC reference number:	**08/H0403/80**

Thank you for your letter of 04 September 2008, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Mental Capacity Act 2005

I confirm that the committee has approved this research project for the purposes of the Mental Capacity Act 2005. The committee is satisfied that the requirements of section 31 of the Act will be met in relation to research carried out as part of this project on, or in relation to, a person who lacks capacity to consent to taking part in the project.

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*	
Application	AB/125008/1	16 April 2008	
Investigator CV		12 December 2007	
Protocol	1.0	09 June 2008	
Peer Review		28 January 2008	
Questionnaire	1.3	03 July 2008	
GP/Consultant Information Sheets	0.7	06 June 2008	
Participant Information Sheet: Parent Vaccination	0.6	02 June 2008	
Participant Information Sheet: Patient	1.3	03 September 2008	
Participant Information Sheet: Relative	1.3	03 September 2008	
Participant Consent Form: Patient	0.93	03 September 2008	
Participant Consent Form: Relative - Assent	0.92	03 July 2009	
Participant Consent Form: Parent	0.7	06 June 2008	
Response to Request for Further Information		04 September 2008	
GP letter (vaccination permission)	0.7	06 June 2008	
GP vaccination form	0.7	06 June 2008	
Response to peer review		07 May 2008	

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

08/H0403/80	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely,

Dr Kate Pointon/Miss Rinat Jibli
Chair/Committee Chair

Email: rinat.jibli@nottspct.nhs.uk

Enclosures: "After ethical review – guidance for researchers"
Site approval form

Copy to: *Sponsor/R&D office for NHS care organisation at lead site – NUH (via email)*

Nottingham Research Ethics Committee 1

LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION

For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.

REC reference number:	08/H0403/80	**Issue number:**	0	**Date of issue:**	09 September 2008
Chief Investigator:	Dr WS Lim				
Full title of study:	A Population based prospective cohort study of pneumococcal pneumonia in adults following the introduction of childhood pneumococcal vaccination in the UK				

This study was given a favourable ethical opinion by Nottingham Research Ethics Committee 1 on 09 September 2008. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.

Principal Investigator	*Post*	*Research site*	*Site assessor*	*Date of favourable opinion for this site*	*Notes* (1)
Dr WS Lim	Consultant Physician	Nottingham University Hospitals NHS Trust	Nottingham Research Ethics Committee 1	09/09/2008	

Approved by the Chair on behalf of the REC:

…… (Signature of Chair/Co-ordinator)
(delete as applicable)

…… (Name)

(1) *The notes column may be used by the main REC to record the early closure or withdrawal of a site (where notified by the Chief Investigator or sponsor), the suspension of termination of the favourable opinion for an individual site, or any other relevant development. The date should be recorded.*

Nottingham University Hospitals NHS Trust

Please reply to: Research and Development
E11 Curie Court
Queen's Medical Centre Campus
Derby Road
Nottingham
NG7 2UH

Telephone: 0115 970 9049
Fax: 0115 849 3295
E-mail:

Dr Wei Shen Lim
Consultant Physician
David Evans Building
City Hospital Campus
Nottingham University Hospitals NHS Trust
Nottingham
NG5 1PB

08 September 2008

Dear Dr Lim

ID: 08RM010 A Population based prospective cohort study of pneumococcal pneumonia in adults following the introduction of childhood pneumococcal vaccination in the UK

The R&D Department has considered the following documents:

. NHS REC Application form, version 5.5.
. Protocol, version 1.0, dated 09.06.08.
. Patient Information Leaflet version 1.3, dated 03/09/2008.
. Parent Information Leaflet version 0.6, dated 02/06/08.
. Relative Information Leaflet version 1.3, dated 03/09/08.
. Consent Form, version 0.93, dated 03/09/2008.
. Parent Consent Form version 0.7, dated 06/06/08.
. Assent Form version 0.92, dated 03/07/2008.
. GP letter (vaccination permission) version 0.7, dated 06/06/08.
. Questionnaire, version 1.3, dated 03/07/2008.
. GP Letter (inclusion), version 0.7, dated 06/06/08.
. GP vaccination form, version 0.7, dated 06/06/08.

Your study now has R&D approval, on the understanding and provision that you will follow the conditions set out below.

Conditions of Approval

That you:

1. Accept the responsibility of Chief/Principal Investigator as defined in the current Research Governance Framework.
2. Request written approval from the R&D department for any change to the approved protocol/study documents you wish to implement.
3. Ensure all study personnel, not employed by the Queens Medical Centre, University Hospital NHS Trust Nottingham or the City Hospital NHS Trust Nottingham, hold honorary Contracts with this Trust, before they have access to any facilities,

patients, staff, their data, tissue or organs.
4. Report any Serious Adverse Event involving the Trust to the R&D department, using the Trust 'policy for research safety reporting in human subjects'. Policy available from the R&D Department.
5. Complete the R&D Research Governance interim and final reports as requested.
6. Comply with the regulatory requirements and legislation relating to: Data Protection, Trust Caldicott Guidelines, Health and Safety and the use of Human Tissue for research purposes.
7. Comply with the current Research Governance Framework, available at www.doh.gov.uk or via the R&D office or Research Governance Web-site.
8. Agree to conduct this research project in accordance with ICH Good Clinical Practice and/or the MRC Guidelines for Good Clinical Practice (as appropriate).
9. Must not start your project until you have received written approval from the relevant ethics committee.

cc Nottingham Research Ethics Committee

Yours sincerely

Dr Brian Thomson
Director of R&D

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