Community-Acquired Pneumonia; Epidemiology and Recovery

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Abstract

Lower respiratory tract infections (LRTIs) represent a spectrum of disease ranging from acute bronchitis to severe community-acquired pneumonia (CAP) and are responsible for 3.2million deaths per year worldwide. Community-acquired pneumonia affects approximately 1% of the UK adult population, with over 100,000 admissions to hospital. Direct healthcare costs are estimated between £441 million and £765 million per year.

Streptococcus pneumoniae is the most frequently identified pathogen in patients with CAP, being directly or indirectly detected in 50% of CAP cases. Streptococcus pneumoniae is an encapsulated gram-positive coccus, with variation in the polysaccharide capsule responsible for differentiation in to more than 90 serotypes. Vaccination programmes against streptococcus pneumoniae have been implemented worldwide to reduce the morbidity and mortality associated with pneumococcal infection. Between 2013 and 2018 a prospective cohort study of adults admitted to a large teaching hospital was conducted, with reference to determining serotype prevalence and clinical risk factors for cases of both invasive and non-invasive pneumococcal disease. Pneumococcal serotype was established using a novel, validated multiplex immunoassay on urine samples that targeted 24 pneumococcal serotypes and cell wall polysaccharide, in combination with blood culture serotype results. During the study period the PCV7 vaccine was replaced by PCV13 vaccine. The results highlighted serotype shift in response to vaccine pressure, with increasing prevalence of non-vaccine serotypes in both invasive and non-invasive pneumococcal disease, as well as deviation away from traditional 'at risk'

cohorts. The study concludes that an up-to-date understanding of prevailing pneumococcal serotypes and the associated 'at risk' populations are fundamental to inform vaccine development, immunisation policy, and clinical practice.

Most of the research in CAP has focussed on timely and accurate diagnosis, optimal management, and risk prediction for traditional outcomes such as mortality and readmission. It has been demonstrated that the majority of patients admitted to hospital with an episode of CAP survive their admission and are discharged to recover in the community. There is a paucity of evidence in the recovery phase, but the available studies highlight a substantial burden of disease for patients during this recovery phase. This thesis aimed to highlight the burden of disease experienced by patients during recovery, develop a consensus on the appropriate tools to employ in future studies of CAP recovery, and explore the feasibility of a specific intervention to improve recovery.

A qualitative study, utilising semi-structured interviews with patients and healthcare providers, to provide a rich description of their ideas, concerns, and experiences of a diagnosis of CAP, its treatment and the associated recovery journey is reported. The study reported that patients were unprepared for the substantial morbidity associated with CAP, consequentially experienced a high degree of anxiety, and frequently re-consulted healthcare providers due to unmet psychosocial needs. Furthermore, healthcare professionals were unaware of the substantial burden that patients experienced and under-appreciated the psychosocial impact of CAP on patients.

Chapters 4 and 5 present the findings of two systematic reviews, conducted according to PRISMA guidelines. The first systematic review outlines patient-reported outcome measures in patients in recovering following hospitalisation for CAP. Patient-reported outcome measures are increasingly recognised as important endpoints in trials and have been recommended for use in studies of drug development. The review demonstrates that a substantial proportion of patients report symptomatic and functional impairments during the first 6 weeks following discharge. The prevalence of symptoms varies across studies in accordance with severity of CAP and age of study cohorts. Persistent symptoms and functional impairment are associated with adverse impacts on the performance of 'normal activities', such as return to work, and healthcare utilisation.

The second systematic review reports 30-day readmission rates and associated risk factors following an episode of hospitalised CAP. Readmission rates have been adopted as surrogate markers of clinical care, but there is limited evidence to determine how and if 30-day readmission rates can be compared within and across different healthcare systems. Thirty-day readmission rate was estimated to be 10% across all included studies. Variation in 30-day readmission was observed by geographic location, whilst estimates of 30-day readmission rate were significantly higher in large database and retrospective studies. Readmissions within 30-days were predominantly pneumonia unrelated, with cardiovascular events accounting for 20% of readmissions. Co-morbid disease,

socio-economic status, and clinical instability at point of discharge were identified as risk factors associated for 30-day readmission.

Given the substantial burden of disease highlighted in the preceding studies, two prospective studies were undertaken at a large teaching hospital in UK.

The first study aimed to determine the tolerability, acceptability, and suitability of individual tools, in different clinically important domains, for the measurement of different aspects of recovery following an episode of hospitalised CAP. Overall, participants demonstrated an improvement in their symptoms, functional ability, and physical capacity from discharge to follow-up at 42-days. The employed assessments demonstrated variable tolerability and acceptability to patients. Questionnaires demonstrated the highest levels of tolerability and acceptability, regardless of whether conducted in-person or remotely. In contrast, assessments of exercise capacity and lung function, requiring attendance at hospital, were less tolerable in the initial days following discharge, with increasing acceptability and tolerability with time from discharge.

The second study sought to determine the safety, tolerability, and acceptability of using an inspiratory muscle training device in the recovery phase of CAP. The study reports that IMT following an episode of CAP was acceptable and tolerable, with side-effects related to IMT were low severity and infrequent, but IMT efficacy is still to be determined.

The thesis highlights the requirement for additional studies in CAP recovery, an area with a substantial paucity of research or evidence on which to base clinical management. These studies should seek to define normal recovery in a large cohort of patients, to derive and validate risk assessment to predict impaired recovery and determine potential targets for novel interventions to alleviate the burden of disease and expedite recovery. Future studies should combine the current knowledge from studies of CAP recovery with the available evidence in recovery following COVID-19 infection.

Publications and other work related to this thesis

Details of manuscripts.

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Pick HJ, Bolton CE, Lim WS, McKeever TM. Patient-reported outcome measures in the recovery of adults hospitalised with community-acquired pneumonia: a systematic review. Eur Respir J. 2019;53(3):1802165. Published 2019 Mar 18. doi:10.1183/13993003.02165-2018

Pick H, Daniel P, Rodrigo C, et al. Pneumococcal serotype trends, surveillance, and risk factors in UK adult pneumonia, 2013-18. Thorax. 2020;75(1):38-49. doi:10.1136/thoraxjnl-2019-213725

Pick HJ, Faghy MA, Creswell G, et al. The feasibility and tolerability of using inspiratory muscle training with adults discharged from the hospital with community-acquired pneumonia. Adv Respir Med. 2021;89(2):216-220. doi:10.5603/ARM.a2021.0002

Lawrence H, Pick H, Baskaran V, et al. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against vaccine serotype pneumococcal pneumonia in adults: A case-control test-negative design study. PLoS Med. 2020;17(10): e1003326. Published 2020 Oct 23. doi: 10.1371/journal.pmed.1003326

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Pick HJ, Ashton D, Tharakan, CS, et al. Experiences, concerns, and needs in recovery from Community-Acquired Pneumonia – a qualitative interview study of patients and healthcare professionals.

Pick HJ, Klukowska A, Ashton D, et al. Readmission rate and associated risk factors for adult patients discharged following an episode of Community-acquired pneumonia; a systematic review and meta-analysis

Pick HJ, Ashton D, Baggot P, et al. Measuring recovery following an episode of Community-Acquired Pneumonia – an exploratory study

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Chapter 1: Introduction

This chapter will outline the importance of community-acquired pneumonia, the commonest infectious cause for hospitalisation in UK, and the associated morbidity and mortality:

1.1) define community-acquired pneumonia (CAP)

1.2) describe the burden of disease, morbidity, and mortality associated with CAP

1.3) outline risk factors for the development of CAP

1.4) describe the epidemiology of CAP with specific reference to pneumococcal disease and the impact of the currently available vaccine options

1.5) describe recovery following an episode of CAP

1.6) outlines the scope of this thesis and briefly summarise the content of subsequent chapters

1.1; Definition of Community-Acquired Pneumonia:

The British Thoracic Society guideline defines Community-acquired pneumonia (CAP) as an acute illness, presenting with symptoms and signs consistent with an acute lower respiratory tract infection (cough and at least one other lower respiratory tract symptom; acute breathlessness, chest pain), in combination with at least one systemic feature (either a symptom complex of sweating, fevers, shivers, aches and pains, and/or temperature of 38°C or more),

associated with new radiographic shadowing for which there is no other explanation (e.g., not pulmonary oedema or infarction), and the illness is the primary reason for hospital admission, is treated as pneumonia, and the patient has not been an inpatient within the preceding 10 days (to exclude cases of hospital-acquired pneumonia).[1]

1.2; Describe the burden of disease, morbidity, and mortality associated with community-acquired pneumonia

Lower respiratory tract infections (LRTIs) are the commonest cause of death from communicable disease worldwide, responsible for 3.2million deaths and superseded only by ischaemic heart disease and stroke.[2] LRTIs represent a spectrum of disease ranging from acute bronchitis to severe community-acquired pneumonia (CAP.) Community-acquired pneumonia is estimated to account for between 5% and 10% of LRTIs presenting to healthcare professionals in the community.[3-5] Approximately 1% of the UK adult population are affected by CAP each year, with over 100,000 admissions to hospital in adults.[6] The incidence of CAP demonstrates a bimodal distribution, with highest incidence reported in children <5 years of age and adults greater than 65 years of age.[4,7] Average length of stay for adult patients hospitalised with CAP is 5 days, with direct healthcare costs in adults estimated between £441 million and £765 million.[3,8,9]

Inpatient mortality rates for CAP vary from approximately 4% to 43%[10,11] depending on disease severity, age, and co-morbid disease.[12-14] The most recent British Thoracic Society (BTS) Adult CAP Audit, using data from 2018-2019, reported an inpatient mortality of 10.4%, down from 20.2% in 2009, whilst 30-day mortality was reported at 13.6%.[15]

1.3; Outline risk factors for the development of CAP

The risk factors associated with CAP development have been summarised by studies.[14,16-20] Non-modifiable risk factors associated with the development of CAP include male sex and advancing age. Modifiable risk factors for CAP can be further divided into co-morbid diseases, lifestyle factors, and prescribed treatments. Co-morbid diseases associated with increased risk of developing CAP include chronic respiratory disease (asthma, COPD, ILD), chronic cardiovascular disease (congestive cardiac failure, cerebrovascular disease), and diabetes mellitus. Lifestyle factors associated with CAP include smoking status (increased risk if current or ex-smoker compared to never smoker), alcohol excess, and nutritional deficiencies including obesity. Immunosuppressive therapies are associated with increased risk of developing CAP, including long-term use of oral corticosteroids, as is the use of gastric acid suppressive drugs.

1.4; Describe the epidemiology of CAP with specific reference to streptococcus pneumonia and the impact of the currently available vaccine options

Multiple different pathogens are implicated in the development of CAP, [21-25] although a specific pathogen will only be identified in approximately 50% of patients despite appropriate microbiological sampling and testing. Streptococcus pneumoniae is the most frequently identified pathogen in patients with CAP,[9,21,26,27] being directly or indirectly detected in 50% of CAP cases.[10] Streptococcus pneumoniae is an encapsulated gram-positive coccus, with variation in the polysaccharide capsule responsible for differentiation in to over 90 serotypes.[28-32] Pneumococcal serotypes have been demonstrated to exhibit different phenotypic characteristics such as relative pathogenicity, potential for invasive infection (bacteraemia), or the development of specific clinical manifestations (such as parapneumonic effusions).[30,31,33]

Pneumococcal conjugate vaccines (PCVs) have demonstrated substantial effectiveness in reducing pneumococcal disease due to vaccine serotypes.[34,35] In England and Wales, immunisation of children with a 7-valent pneumococcal conjugate vaccine (PCV7) commenced in 2006 and was replaced in April 2010 with a 13-valent pneumococcal conjugate vaccine (PCV13).[36] Over the same period, individuals aged >2 years with a clinical risk factor for pneumococcal disease and all adults aged ≥65 years have been offered vaccination with the 23-valent pneumococcal polysaccharide vaccine (PPV23).[36]

Both PCVs have been associated with rapid and sustained reductions in overall and vaccine-serotype invasive pneumococcal disease (IPD) in young children.[37]

PCVs also reduce carriage in vaccinated individuals and hence prevent onward transmission to unvaccinated older children and adults. Thus, reductions in IPD and pneumococcal pneumonia have been observed across all age groups.[37-40]

Since 2013/14, however, overall IPD incidence due to PCV13 serotypes has plateaued in the UK, while IPD due to non-PCV serotypes has increased rapidly, especially in adults and the elderly.[35,37] The USA by contrast, where PCV13 has been recommended as part of the childhood immunisation programme since 2010, has not observed such an increase in non-PCV13-serotype IPD despite large declines in PCV13-serotype disease.[41]

In adults, IPD accounts for less than 10% of pneumococcal pneumonia cases. There are therefore limited contemporary data on the range of serotypes causing pneumococcal pneumonia in adults in the UK.[40] In particular, the contribution of PCV13 and PPV23 serotypes to pneumococcal pneumonia is important to inform national pneumococcal vaccine policy, especially in adults and the elderly.[42,43]

Since 2008, a prospective population-based adult pneumococcal pneumonia study has been conducted at Nottingham University Teaching Hospitals NHS Trust to determine changes in clinical disease and the responsible pneumococcal serotypes.[28,40]

1.5; Describe the burden of disease in recovery following an episode of CAP

It follows, based on the most recent British Thoracic Society CAP Audit report, that approximately 90% of patients are expected to survive their acute admission for an episode of CAP.[15] These patients are subsequently discharged back in to the community for convalescence, frequently with persistent symptoms and functional impairment, often not in keeping with traditional measures of cure. There is, therefore, disparity between physician-rated clinical cure, radiographic resolution, and patient-reported symptom resolution, including return to function.[44]

In practice, a patient is generally deemed to have recovered from CAP based mainly on the clinical assessment of a physician, often in association with radiological improvement/resolution on a follow-up chest radiograph. In a randomised controlled trial of CAP patients receiving usual therapy with adjunctive corticosteroids or placebo, clinical cure at 30 days was 77.5% in placebo group.[45]Furthermore, in a multi-centre study by Bruns et al 288 adult patients admitted to hospital with severe CAP were assessed for clinical cure and radiological resolution at 28 days following discharge. Clinical cure was observed in 78% of participants, and radiological resolution in 53%.[46] In addition, another study reported radiographic resolution at 14 and 28 days following discharge as 50.6% and 66.7% respectively.[47]

However, patient-reported symptoms following admission with CAP persevere, and may take weeks or months to resolve; three out of four patients report the persistence of at least 1 symptom at 28 days following discharge,[48-54] whilst

median time for return to ADLs ranges from 15 to 24 days,[49,50,55,56] and in those currently in employment the median time for return to work is approximately 14 days,[54,56] Normal recovery from CAP is poorly defined and there are no widely agreed set of outcome measures for its evaluation. The lack of appropriate research in this field is reflected in a poor understanding of:

- the relationship between patient-reported symptoms and biological, physiological, or cognitive markers of pathology,[48-64]
- the mechanisms that underlie recovery from pneumonia
- Possible interventions that may improve recovery from pneumonia, including the avoidance of unnecessary antibiotic use during recovery.

1.6; Thesis Outline

This thesis will consider patients with hospitalised CAP, defined as patients presenting to secondary care with signs and symptoms consistent with a lower-respiratory tract infection, with radiographic confirmation of consolidation, and treated as CAP by the attending medical team.

The aim of the thesis is broadly divided in two; 1) to outline the circulating serotypes responsible for pneumococcal CAP in hospitalised adults and the associated implications for vaccine policy, and 2) to describe the burden of disease in recovery following an episode of hospitalisation with CAP.

Chapter 2 reports the findings of a prospective cohort study of adults admitted to a large teaching hospital in UK between 2013 and 2018. Patients with clinical features of LRTI, radiologically confirmed consolidation, and treated by the admitting clinician as CAP were eligible for inclusion. Following participant consent, patient demographic, clinical, and outcome data were collected using a standardised proforma. Urine samples were collected from all included patients and tested for pneumococcal aetiology using Binax Now. Pneumococcal serotype was established using a new, validated multiplex immunoassay targeting 24 pneumococcal serotypes and cell wall polysaccharide, in combination with blood culture serotype results.

There are two types of pneumococcal vaccine licensed in the UK to provide protection against infection with different pneumococcal serotypes. The polysaccharide vaccine (PPV23) contains purified capsular polysaccharide from 23 common pneumococcal serotypes and most adults develop a good antibody

response to PPV23 after 3 weeks of immunisation. The pneumococcal conjugate vaccines (PCV7, PCV10, PCV13) contain polysaccharides derived from 7, 10, or 13 of the common capsular types. The polysaccharides from the capsular types are conjugated to proteins and this has been demonstrated to increase immunogenicity in children.

During the study period the PCV7 vaccine was replaced by PCV13 vaccine. Previous studies have demonstrated that serotype distribution changes following the introduction of conjugate vaccines to immunisation schedules. National IPD surveillance data in UK has reported rapid expansion of non-vaccine serotypes, however invasive disease comprises only 10% on all cases pneumococcal pneumonia, and contemporaneous data for non-invasive disease is reported in chapter 2.

Chapter 3 describes a qualitative study in patients recovering following a hospital admission for radiographically confirmed CAP. Semi-structured patient interviews provide a rich description of their ideas, concerns, and experiences of a diagnosis of CAP, its treatment, and the associated recovery journey. In addition, the study reports the experiences and perspective of healthcare professionals caring for patients with CAP, focussing on their knowledge and expectations of the recovery phase following discharge from hospital.

Chapter 4 presents the findings of a systematic review, conducted according to PRISMA guidelines, of patient-reported outcome measures in patients in recovery following hospitalisation for CAP. Patients experience a substantial burden of disease during their recovery which is not captured by conventional

outcome measures such as 30-day mortality and readmission. Patient-reported outcome measures are increasingly recognised as important endpoints in trials and have been recommended for use in studies of drug development. A recent review of outcome measures across diagnosis, investigation, management, and recovery in CAP recommended only one patient-reported outcome measure, the CAP-symptom score. Little is known about normal recovery following CAP, the optimum measures in recovery, nor the tools for their assessment.

Chapter 5 reports a second systematic review in patients with CAP, focussing on 30-day readmission rate the associated risk factors for readmission. The objective of the systematic review was to provide a summary of hospital readmission following an initial episode of hospitalised CAP to allow comparison within and between healthcare systems and structures, as well as identifying risk factors for readmission which would facilitate the development of novel, targeted interventions to reduce readmission rates.

Chapters 6 and 7 report the results of two prospective exploratory cohort studies conducted at a large teaching hospital in UK. Both investigated recovery in adults discharged from hospital following a radiologically confirmed episode of CAP; the first study conducted assessments across multiple distinct domains of recovery to determine tolerability, acceptability, and suitability of individual tools to inform the development of future cohort studies to define normal recovery, whilst the second study sought to determine the safety, tolerability, and acceptability of using an inspiratory muscle training device in the recovery phase of CAP.

Chapter 8 draws together the included body of work, summarising the important results for pneumococcal serotype trend and CAP recovery, the associated implications and recommendations for clinical practice and vaccine policy, and suggested future research priorities in CAP recovery.

Chapter 2: Pneumococcal serotype trends, surveillance, and risk factors in UK adult pneumonia, 2013-2018

2.1; Introduction

As outlined earlier, pneumococcal conjugate vaccines (PCVs) have demonstrated substantial effectiveness in reducing pneumococcal disease due to vaccine serotypes across all age groups and in multiple countries. [34,35,37-40] However, since 2013/14, overall IPD incidence due to PCV13 serotypes has plateaued in the UK, while IPD due to non-PCV serotypes has increased rapidly, especially in adults and the elderly.[35,37] It has been demonstrated that IPD accounts for less than 10% of pneumococcal pneumonia cases. There are therefore limited contemporary data on the range of serotypes causing pneumococcal pneumonia in adults in the UK.[40] In particular, the contribution of PCV13 and PPV23 serotypes to pneumococcal pneumonia is important to inform national pneumococcal vaccine policy, especially in adults and the elderly.[42,43]

The Respiratory Infection Research Group in Nottingham has conducted a prospective population-based adult pneumococcal pneumonia study to determine changes in clinical disease and the responsible pneumococcal serotypes since 2008.[28,40] Recently, a novel, validated 24-valent multiplex urinary immunoassay was developed to detect PCV and PPV serotypes in patients with non-invasive disease.[65] This chapter reports the use of this assay in a previously unreported cohort of patients to describe a) serotype trends in adult pneumococcal pneumonia since PCV13 replaced PCV7, and b) the clinical risk groups associated with vaccine-type disease.

2.2; Methods

2.2.1; Study design

This prospective observational cohort study of consecutive adult patients admitted to two large university hospitals with CAP was conducted between September 2013 and August 2018. Together, these two hospitals cover the catchment for emergency admissions in the Greater Nottingham area. All patients admitted to acute admission areas were screened for study eligibility every weekday. Patients aged ≥16 years presenting with one or more symptom suggestive of lower respiratory tract infection (LRTI; defined as cough, increasing dyspnoea, sputum production, and fever), with evidence of acute infiltrates consistent with respiratory infection on admission radiography, and treated for a diagnosis of CAP were eligible. Exclusion criteria included hospitalisation within 10 days of index admission, a diagnosis of tuberculosis, or post-obstructive pneumonia. Informed consent was obtained from all study participants; if patients lacked capacity, proxy consent was sought from patient personal consultees. Demographic and clinical characteristic data were collected using a standardised proforma. Study procedures were approved by the Nottingham Research Ethics Committee (REC reference 08/H0403/80) (Appendix 3).

2.2.2; Microbiology

Baseline microbiological investigations were performed at the discretion of the clinical team. In addition, urine samples for pneumococcal specific microbiological analyses were obtained within 72 hours of admission; Binax-NOW® (Alere, Stockport, UK) assay for pneumococcal C-polysaccharide urinary antigen detection (UAD) was performed in the local microbiological laboratory,[66] with the remaining volume of urine frozen at -80°C and batch transported to Public Health England (PHE)'s Respiratory and Vaccine Preventable Bacteria Reference Unit (RVPBRU) in Colindale, London for pneumococcal serotyping using a validated multiplex immunoassay (Bio-plex24.) The Bio-plex24 assay targets the detection of pneumococcal serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F, and the pneumococcal cell-wall polysaccharide.[65] Samples from September 2014 to August 2015 were tested using the original protocol as published by Eletu et al, with a clinical sensitivity of 96·2%, specificity 89·9%.[65] The assay was then updated to include minor protocol modifications and alternative monoclonal clones for serotypes 7F, 18C, 19F, 20, and 22F; this updated assay (validated using 2037 urine samples from patients with CAP or suspected pneumococcal disease, with a calculated clinical sensitivity of 94·3% and specificity of 93·6% - manuscript in preparation) was used for the remainder of the study period. Sixteen of the human monoclonal antibodies within the Bio-plex24 assay exhibit some cross-reactivity with specific non-targeted pneumococcal serotypes. A 'checkerboard' system for interpretation of results allows serotype identification for 5 of these serotypes. In the remaining 11, based on probabilistic grounds, the

designated serotype for analysis was determined according to the predominant serotype observed in national IPD data for the corresponding period (Table 2.1).[37]

Table 2-1: Target serotypes for human-Monoclonal Antibodies (h-MAAb), associated cross-reactivity, Bio-plex24 immunoassay reporting, and final serotype designation;

h-MAAb target	Serotype(s) with which h-MAb cross-reacts	Bio-plex24 result	Final serotype designation
1	n/a	1	1
2	n/a	2	2
3	n/a	3	3
4	n/a	**4**	**4**
5	n/a	**5**	**5**
6A	6B, 6C, 6D	6A/C	**6C**
6B	6A, 6D	6B/D	**6B**
7F	**7A**	7F/A	**7F**
8	n/a	8	8
9N	9L, 18A, **43**, **47A**	9N	9N
9V	9A, 9L	9A/V	**9V**
10A	10B, 10C, 10F, 33C, 39	Group 10 or 33C or 39	**10A**
11A	11C, 11D, 11E, 16A, 16F, 18A, 18B, 18C	11A/C/E or Group 16	**11A**
12F	12B, 22A, **44**	12F or **44** or 22A	**12F**
14	9L, 9N	**14**	14
15B	15A, 15C, 15F, 11D, 12B, 18A	Group 15	**15A**
17F	n/a	17F	17F
18C	18A, 18B, 18F	18B/C/F	**18C**
19A	19F, 9A, 9L, 9V, 18B, 18C	19A	19A
19F	19A, 19B, 19C	Group 19	19F
20	n/a	20	20
22F	6C, 6D, 20	22F	22F
23F	32A, 32F	23F or Group 32	**23F**
33F	33A, 33B, 33D	33A/B/D/F	**33F**

h-MAAb: human monoclonal antibody; Bold indicates final serotype designation based on predominant serotype identified in national invasive pneumococcal disease surveillance data. For 16 of 24 targeted serotypes, the h-MAAb exhibit cross reactivity for non-targeted pneumococcal serotypes. When a h-MAAb cross reacts with another targeted serotype this can be taken into consideration for interpretation of results. Consequentially, definitive serotype designations can be achieved for 13 serotypes, with serogroup combinations reported for the remaining 11 targeted serotypes. For serogroup combinations, a final serotype designation has been achieved based on the predominant serotype derived from corresponding national invasive pneumococcal disease surveillance data.

During sample testing between September 2014 and August 2015 (first batch tested), the monoclonal antibodies targeting serotypes 7F, 20, and 22F were found to cross-react with an unknown substance in some urine samples. Therefore, in reporting results for samples from that study year, all results for serotype 7F were excluded and a higher diagnostic threshold for serotypes 20 and 22F was applied, with results excluded if these criteria were not satisified.[65] Samples from the four other study years were tested with an improved Bio-plex24 assay, outlined above, eliminating the non-specific cross-reactivity.

Up to September 2017, bacteraemic isolates of *Streptococcus pneumoniae* were identified by standard phenotypic methods and serotyped by slide agglutination tests with latex antisera (ImmuLex™ Pneumotest kit) or standard factor sera (SSI Diagnostica, Denmark). From October 2017, confirmation of pneumococcal isolate identification and serotype prediction was performed by bio-informatical methods following DNA extraction and whole genome sequencing,[67] with the exception of serotypes within serogroup 24 which were identified by conventional methods using antisera.[68]

Patients were considered to have pneumococcal CAP if any of the following criteria were met: a) positive pneumococcal UAD or b) a positive blood culture for *S pneumoniae* or c) pneumococcal serotype or cell wall polysaccharide detection by the Bio-plex24 assay.

2.2.3; Statistical methods

Serotypes were classified according to the serotype content of vaccines: PCV7 serotypes (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F), PCV13non7 serotypes (serotypes 1, 3, 5, 6A/C, 7F/A, 19A), PPV23non13 serotypes (serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F), and non-vaccine-type (NVT) serotypes (comprising a) any non-PCV13, non-PPV23 serotype and b) 'untyped' pneumococcal disease; Binax UAD positive without subsequent serotype identification, or Bio-plex24 positive for cell wall polysaccharide only.)

Annual incidence rates were derived from mid-year estimates from the Office for National Statistics for the Greater Nottingham area, including local population data stratified by age group (16-49, 50-64, 65-74, 75-84, and ⩾85 years.) Trends between 2013 and 2018 comparing overall incidence of CAP, pneumococcal CAP, and CAP according to serotype categories were examined. Additionally, serotype trends were compared with corresponding national IPD surveillance data.[37] Poisson regression models together with 95% confidence intervals were used to assess year to year variation and linear trends in serotype distribution.

Clinical risk factors for pneumococcal disease were defined in accordance with PHE's 'Immunisation against Infectious Diseases' (The Green Book).[36] For analyses of groups at-risk of pneumococcal disease, patients with multiple serotypes that crossed vaccine groups were excluded (e.g. one or more positive serotype in both PCV-13 and PPV23-serotype disease groups). Baseline characteristics and co-morbid risk factors for PCV13- and PPV23-serotype disease were compared using Pearson's chi-square or Fisher's exact tests for

categorical variables, and the Mann-Whitney U test for non-parametric continuous variables. Likelihood ratio tests were used to determine the best model fit for continuous variables. Multivariable logistic regression was used to compare the independent association between co-morbid disease and a) PCV13- and b) PPV23-serotype disease. Purposeful selection of variables for inclusion in the multivariable analysis was conducted based on clinical risk factors outlined in PHE's 'Immunisation against Infectious Diseases' (The Green Book),[36] in conjunction with evidence from previous studies of risk factors for pneumococcal and/or vaccine serotype disease, and considering biological plausibility, and were specified *a priori*.[69] These a priori variables included chronic respiratory disease including asthma and COPD, chronic heart disease, chronic kidney disease, chronic liver disease, immunosuppression (including splenic dysfunction, haematological disease including malignancy, solid organ or bone-marrow transplant, immunodeficiency, HIV, or treatment with immunosuppressive therapies but not steroids), diabetes mellitus requiring therapy, and individuals with cerebrospinal fluid (CSF) leaks or cochlear implants.

Secondary analyses were conducted examining the risk of PCV13- and PPV23-serotype disease in:

(a) the pneumococcal clinical risk group (defined as adults 16-64 years with ≥1 clinical risk factor for pneumococcal disease or age ≥65 years),

(b) specific clinical risk groups: (1) aged 16-64 years without clinical risk factors, (2) aged 16-64 years with ≥1 clinical risk factor, (3) aged ≥65 years without clinical risk factors, and (4) aged ≥65 years with ≥1 clinical risk factor, and

(c) Individuals with increasing numbers of clinical risk factors.

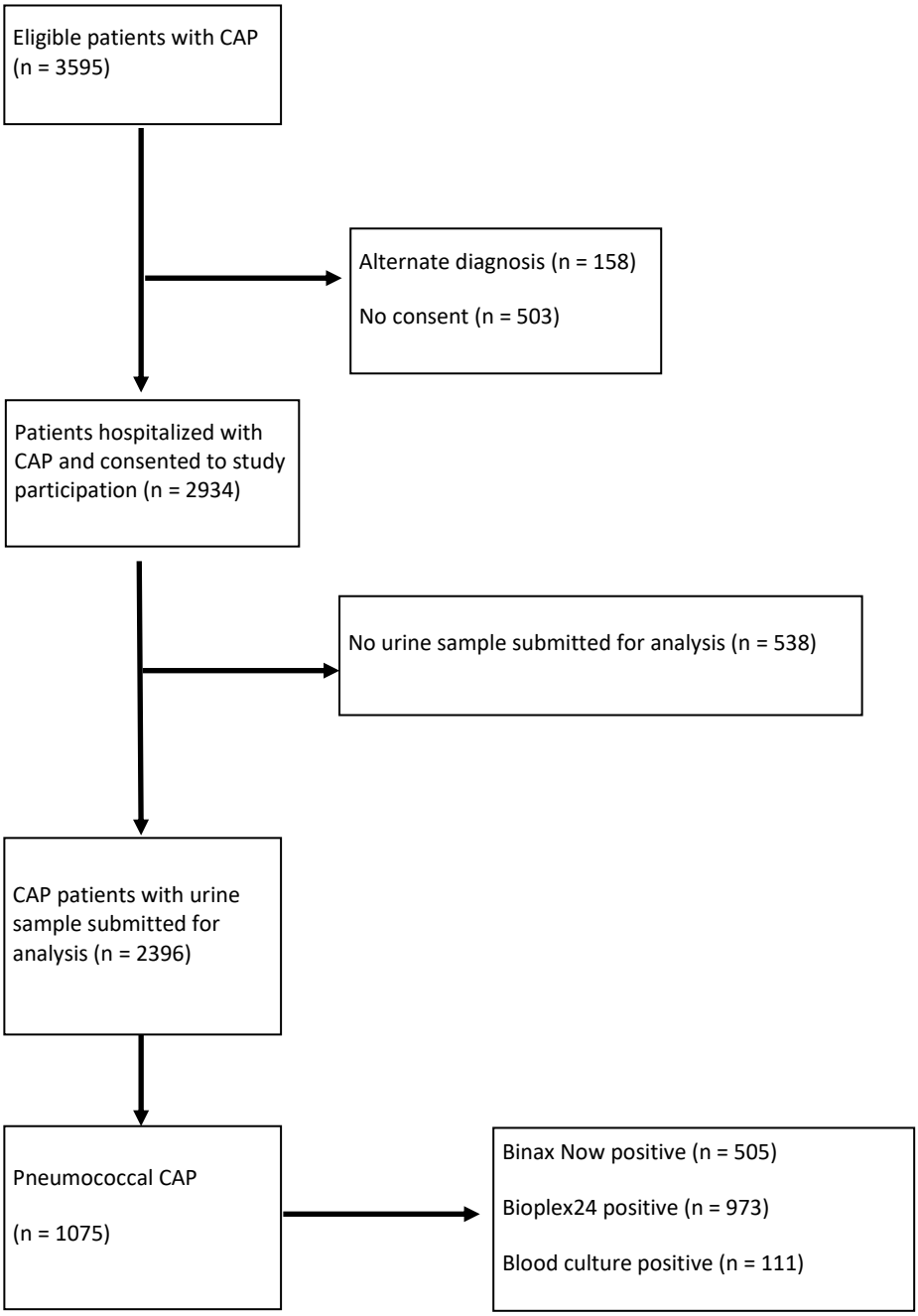
Sensitivity analyses were conducted to investigate the impact of a) the method used for serotype designation and b) serotype 3 disease. Statistical analyses were conducted using Stata/IC 15 (©StataCorp. 2017).

2.3; Results

2.3.1; Study population

During the five-year study period, of 3595 eligible patients, 158 (4·4%) patients had an alternative diagnosis and study consent was not obtained for 503 (14·6%)(Figure 2.1). Patients without consent were older (median age 82·2 years, interquartile range (IQR) 70·2-88·9 years versus 71·3 years, IQR 55·8-81·2 years, p<0·001), more often resident in care home facilities (35·0% versus 4·0%, p<0·001), more likely to have chronic kidney disease (12·8% versus 8·3%, p=0·001), cerebrovascular disease (21·2% versus 7·7%, p<0·001), and cognitive impairment (33·6% versus 3·7%, p<0·001), and less likely to have chronic respiratory disease (19·5% versus 27·9%, p<0·001) compared to the study cohort patients.

Figure 2-1: Study flow diagram



2.3.2; Baseline characteristics

The study cohort consisted of 2934 adults hospitalised with CAP between 2013 and 2018 (Table 2.2); median age 71·3 years (IQR 55·8-81·2 years), 1515 (51·7%) male, and pneumonia severity low, moderate, and high in 1377 (46·9%), 880 (30·0%), and 677 (23·1%) patients respectively. Admission to intensive care occurred in 225 (7·7%) cases and overall 30-day case mortality rate was 7·5% (n= 219).

In 538 of 2934 patients, a urine sample was not available for pneumococcal testing. *Streptococcus pneumoniae* was identified in 1075 (36.6%) patients; Binax-NOW® test was positive in 505 (47·0%) of 1075, Bio-plex24 in 973 (90·5%) and blood cultures in 111 (10·3%). One or more serotype was determined in 843 (78·4%) of 1075 patients with pneumococcal CAP; 2 serotypes were identified in 102 patients and ≥3 serotypes in 15 patients.

Table 2-2: Baseline characteristics, disease severity, and outcomes for CAP cohort and pneumococcal CAP cohort

	CAP cohort	Pneumococcal CAP cohort
Patients	2934	1075
Demographics		
Age, years (IQR)	71·3 (55·8-81·2)	69·3 (53·9-80·1)
16-49 years	522 (17·8)	214 (20·0)
50-64 years	590 (20·1)	228 (21·2)
65-74 years	610 (20·8)	246 (22·9)
75-84 years	757 (25·8)	226 (21·0)
⩾85 years	455 (15·5)	161 (14·9)
Male	1515 (51·7)	513 (47·8)
Care Home Resident	116 (4·0)	35 (3·3)
Comorbid disease		
Never smoker[#]	836 (29·5)	292 (28·0)
Ex-smoker[#]	1311 (46·3)	438 (42·0)
Current smoker[#]	685 (24·1)	314 (30·1)
Alcohol excess	80 (2·7)	42 (3·9)
Malignancy	269 (9·2)	91 (8·5)
Liver disease	48 (1·6)	24 (2·2)
Kidney disease	244 (8·3)	83 (7·7)
Chronic heart disease	460 (15·7)	145 (13·5)
Congestive cardiac failure	185 (6·3)	64 (6·0)
Ischaemic heart disease	321 (10·9)	101 (9·4)
Chronic lung disease (excluding asthma)	819 (27·9)	292 (27·2)
COPD	723 (24·6)	261 (24·3)
Asthma	312 (10·6)	122 (11·4)
Diabetes Mellitus	469 (16·0)	163 (15·2)
Cerebrovascular disease	225 (7·7)	82 (7·6)
Cognitive impairment	107 (3·7)	36 (3·4)
Immunocompromise	109 (3·7)	47 (4·4)
Disease Severity		
CURB-65 0-1	1377 (46·9)	483 (44·9)
CURB-65 2	880 (30·0)	320 (29·8)
CURB-65 ⩾3	677 (23·1)	272 (25·3)
Outcomes		
Critical Care admission	225 (7·7)	108 (10·1)
30-day mortality	219 (7·5)	54 (5·0)

Data are presented as n (%) or median (interquartile range). COPD: chronic obstructive pulmonary disease; CURB-65: confusion, urea >7 mmol.L^{-1}, respiratory rate >30 breaths.min^{-1}, blood pressure <90mmHg [systolic] <60mmHg [diastolic], age ⩾65years. #: Data regarding smoking status available for 2832 and 1040 participants in the CAP cohort and Pneumococcal CAP cohort respectively.

2.3.3; Trends in pneumococcal CAP

The overall annual incidence of CAP over the study period was 120·4 (95% confidence interval (CI) 116·4-124·5) per 100,000 population. Annual incidence rates are presented in Table 2.3. Incidence increased significantly over the five-year period (annual IRR 1·12, 95% CI 1·09-1·14, p<0·001) (Table 2.4). Adults aged ⩾85 years demonstrated the greatest relative increase (115%) between 2013 and 2018 (annual IRR 1·24, 95% CI 1·17-1·31, p<0·001).

The overall annual incidence of pneumococcal CAP was 37·7 (95% CI 35·3-39·8) per 100,000 population. Pneumococcal CAP incidence rates increased over five years particularly in older age groups; for adults aged 65-74 years, 75-84 years, and ≥85years, annual IRR was 1·12 (95% CI 1·02-1·22, p=0·014), 1·20 (95% CI 1·09-1·32, p<0·001), and 1·15 (95% CI 1·03-1·28, p=0·014), respectively.

Table 2-3: Incidence rates of community-acquired pneumonia (CAP), pneumococcal CAP, and CAP due to vaccine and non-vaccine groups by study year

	Patient age, years	Year 6, 2013-2014			Year 7, 2014-2015 *			Year 8, 2015-2016			Year 9, 2016-2017			Year 10, 2017-2018		
		n	Incidence #	95% CI	n	Incidence #	95% CI	n	Incidence #	95% CI	n	Incidence #	95% CI	n	Incidence #	95% CI
All CAP		538	96·3	88·4-104·8	688	120·9	112·1-130·3	548	95·8	88·0-104·2	744	129·3	120·2-139·0	919	158·4	148·4-169·0
	16-49	91	27·3	22·0-33·5	117	34·8	28·8-41·7	114	33·7	27·8-40·5	112	33.0	27·1-39·7	102	29·9	24·4-36·3
	50-64	93	80·2	64·7-98·2	127	107·6	89·7-128·1	114	94·9	78·3-114·0	145	119·7	101·0-140·8	180	146·9	126·3-170·0
	65-74	105	181·3	148·3-219·5	148	248·7	210·3-292·2	101	164·2	133·7-199·5	131	210·4	175·9-249·6	194	310·4	268·3-357·3
	75-84	145	400·6	338·0-471·3	181	495·9	426·3-573·6	142	386·9	325·9-456·0	199	541·3	468·7-622·0	207	559·5	845·8-641·1
	≥85	104	707·5	578·1-857·2	115	766·7	633·0-920·3	77	505·4	398·9-631·7	157	1024·1	870·2-1197·5	236	1522·6	1334·5-1729·7
Pneumococcal CAP		180	32·2	27·7-37·3	200	35·2	30·5-40·4	166	29.0	24·8-33·8	247	42·9	37·7-48·6	282	48·6	43·1-54·6
	16-49	45	13·5	9·8-18·0	46	13·7	10·0-18·3	36	10·6	7·5-14·7	46	13·5	9·9-18·1	41	12.0	8·6-16·3
	50-64	36	31.0	21·7-43·0	40	33·9	24·2-46·2	37	30·8	21·7-42·5	55	45·4	34·2-59·1	60	49.0	37·4-63·0
	65-74	38	65·6	46·4-90·1	48	80·7	59·5-107·0	41	66·6	47·8-90·4	50	80·3	59·6-105·9	69	110·4	85·9-139·7
	75-84	28	77·3	51·4-111·8	45	123·3	89·9-165·0	34	92·6	64·2-129·5	59	160·5	122·2-207·0	63	170·3	130·8-217·8
	≥85	33	224·5	154·5-315·3	21	140.0	86·7-214·0	21	137·8	85·3-210·7	37	241·4	170·0-332·7	49	316·1	233·9-417·9
PCV7-serotype CAP		10	1·8	0·9-3·3	14	2·5	1·3-4·1	12	2·1	1·1-3·7	17	3.0	1·7-4·7	18	3·1	1·8-4·9
	16-49	1	0·3	0·0-1·7	2	0·6	0·1-2·2	3	0·9	0·2-2·6	2	0·6	0·1-2·1	1	0·3	0·0-1·6
	50-64	1	0·9	0·0-4·8	1	0·8	0·0-4·7	2	1·7	0·2-6·0	1	0·8	0·0-4·6	2	1·6	0·2-5·9
	65-74	3	5·2	1·1-15·1	3	5.0	1·0-14·7	3	4·9	1·0-14·2	6	9·6	3·5-21·0	5	8.0	2·6-18·7
	75-84	1	2·8	0·1-15·4	6	16·4	6·0-35·8	2	5·4	0·7-19·7	3	8·2	1·7-23·9	6	16·2	6·0-35·3
	≥85	4	27·2	7·4-69·7	2	13·3	1·6-48·2	2	13·1	1·6-47·1	5	32·6	10·6-76·1	4	25·8	7·0-66·1
PCV13non7-serotype CAP		64	11·5	8·8-14·6	56	9·8	7·4-12·8	51	8·9	6·6-11·7	88	15·3	12·3-18·8	90	15·5	12·5-19·1
	16-49	15	4·5	2·5-7·4	4	1·2	0·3-3·0	7	2·1	0·8-4·3	11	3·2	1·6-5·8	5	1·1	0·5-3·4
	50-64	15	12·9	7·2-21·3	8	6·8	2·9-13·4	11	9·2	4·6-16·4	14	11·6	6·3-19·4	23	18·8	11·9-28·2
	65-74	14	24·2	13·2-40·6	21	35·3	21·8-54·0	14	22·8	12·4-38·2	21	33·7	20·9-51·6	23	36·8	23·3-55·2
	75-84	12	33·1	17·1-57·9	13	35·6	19·0-60·9	8	21·8	9·4-43·0	29	78·9	52·8-113·3	22	59·5	37·3-90·0
	≥85	8	54·4	23·5-107·2	10	66·7	32·0-122·6	11	72·2	36·0-129·1	13	84·8	45·2-145·0	17	109·7	63·9-175·6

Table 2-3: Incidence rates of community-acquired pneumonia (CAP), pneumococcal CAP, and CAP due to vaccine and non-vaccine groups by study year (continued)

	Patient age, years	Year 6, 2013-2014			Year 7, 2014-2015 *			Year 8, 2015-2016			Year 9, 2016-2017			Year 10, 2017-2018		
		n	Incidence #	95% CI	n	Incidence #	95% CI	n	Incidence #	95% CI	n	Incidence #	95% CI	n	Incidence #	95% CI
PPV23non13-serotype CAP		71	12·7	9·9-16·0	93	16·3	13·2-20·0	73	12·8	10·0-16·0	99	17·2	14·0-21·0	95	16·4	13·3-20·0
	16-49	19	5·7	3·4-8·9	27	8.0	5·3-11·7	20	5·9	3·6-9·1	23	6·8	4·3-10·2	21	6·1	3·8-9·4
	50-64	16	13·8	7·9-22·4	19	16·1	9·7-25·1	19	15·8	9·5-24·7	21	17·3	10·7-26·5	20	16·3	10·0-25·2
	65-74	13	22·5	12·0-38·4	17	28·6	16·6-45·7	16	26.0	14·9-42·2	20	32·1	19·6-49·6	22	35·2	22·1-53·3
	75-84	13	35·9	19·1-61·4	21	57·5	35·6-87·9	12	32·7	16·9-57·1	21	57·1	35·4-87·3	19	51·4	30·9-80·2
	≥85	10	68.0	32·6-125·1	9	60.0	27·4-113·9	6	39·4	14·4-85·7	14	91·3	49·9-153·2	13	83·9	44·7-143·4
Non-vaccine-serotype CAP		50	9.0	6·6-11·8	55	9·7	7·3-12·6	47	8·2	6·0-10·9	70	12·2	9·5-15·4	99	17·1	13·9-20·8
	16-49	12	3·6	1·9-6·3	15	4·5	2·5-7·4	10	3.0	1·4-5·4	13	3·8	2·0-6·5	13	3·8	2·0-6·5
	50-64	9	7·8	3·5-14·7	13	11.0	5·9-18·8	7	5·8	2·3-12·0	21	17·3	10·7-26·5	19	15·5	9·3-24·2
	65-74	12	20·7	10·7-36·2	13	21·8	11·6-37·4	11	17·9	8·9-32·0	12	19·3	10·0-33·7	25	40.0	25·9-59·0
	75-84	4	11.0	3·0-28·3	11	30·1	15·0-53·9	11	30.0	15·0-53·6	16	43·5	24·9-70·7	22	59·5	37·3-90·0
	≥85	13	88·44	47·1-151·2	3	20.0	4·1-58·4	8	52·5	22·7-103·4	8	52·2	22·5-102·8	20	129.0	78·8-199·3

PCV7-serotype CAP: CAP due to serotypes included in PCV7; PCV13non7-serotype CAP: CAP due to serotypes included in PCV13, excluding serotypes also included in PCV7; PPV23non13-serotype CAP: CAP due to serotypes included in PPV23, excluding serotypes also included in PCV13; Non-vaccine-serotype CAP: CAP due to a) any non-PCV13-non-PPV23-serotype and b) untyped pneumococcal cases – blood culture or BINAX UAD positive without subsequent serotype identification, or Bio-plex24 assay positive for cell wall polysaccharide only.. #: per 100,000 population

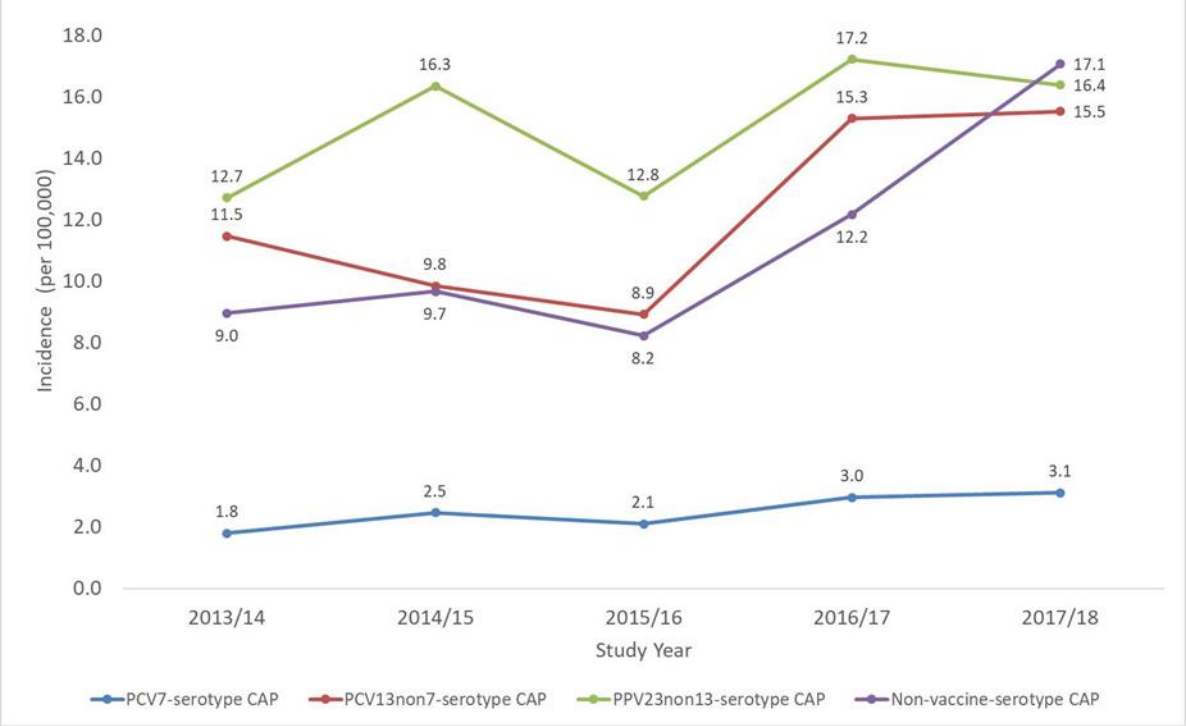
Table 2-4: Linear trends and variation in CAP due to serotype groups, and non-vaccine serotype CAP

	2013-14	2014-15		2015-16		2016-17		2017-18		Change in IRR per year		p value for trend
	IRR	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI		95% CI	
All CAP	1·0	1·26	1·12-1·41	0·99	0·88-1·12	1·34	1·20-1·50	1·64	1·48-1·83	1·12	1·09-1·14	**<0·001**
Pneumococcal CAP	1·0	1·09	0·89-1·33	0·9	0·73-1·11	1·33	1·10-1·61	1·49	1·23-1·79	1·11	1·06-1·16	**<0·001**
PCV7-serotype CAP	1·0	1·37	0·61-3·09	1·17	0·51-2·71	1·65	0·76-3·60	1·73	0·80-3·75	1·13	0·96-1·34	0·135
PCV13non7-serotype CAP	1·0	0·86	0·60-1·23	0·78	0·54-1·12	1·33	0·97-1·84	1·35	0·98-1·87	1·12	1·04-1·21	**0·003**
PPV23non13-serotype CAP	1·0	1·29	0·94-1·75	1.00	0·72-1·39	1·35	1·0-1·84	1·29	0·95-1·75	1·06	0·99-1·13	0·112
Non-vaccine-serotype CAP	1·0	1·08	0·74-1·58	0·92	0·62-1·37	1·36	0·95-1·95	1·91	1·36-2·68	1·19	1·10-1·28	**<0·001**

Data are presented as incidence rate ratio (IRR) with 95% confidence intervals. PCV7-serotype CAP: CAP due to serotypes included in PCV7; PCV13non7- serotype CAP: CAP due to serotypes included in PCV13, excluding serotypes also included in PCV7; PPV23non13 -serotype CAP: CAP due to serotypes included in PPV23, excluding serotypes also included in PCV13; Non-vaccine -serotype CAP: CAP due to a) any non-PCV13-, non-PPV23- serotype and b) untyped pneumococcal cases – blood culture or BINAX UAD positive without subsequent serotype identification, or Bio-plex24 assay positive for cell wall polysaccharide only.

The overall annual incidence for CAP due to PCV7, PCV13non7, PPV23non13 and NVTs was 2·5 (95% CI 1·9-3·1), 12·2 (95% CI 11·0-13·6), 15·1 (95% CI 13·7-16·6), and 11·2 (95% CI 10·0-12·5) per 100,000 population, respectively (Figure 2.2). The incidence of PCV13non7-serotype CAP (annual IRR 1·12, 95% CI 1·04-1·21, P=0·003) and NVT-serotype CAP (annual IRR 1·19, 95% CI 1·10-1·28, P<0·001) increased significantly over five years.

Figure 2-2: Incidence of serotyped pneumococcal CAP by vaccine groups between 2013 and 2018. Incidence per 100,000 adult

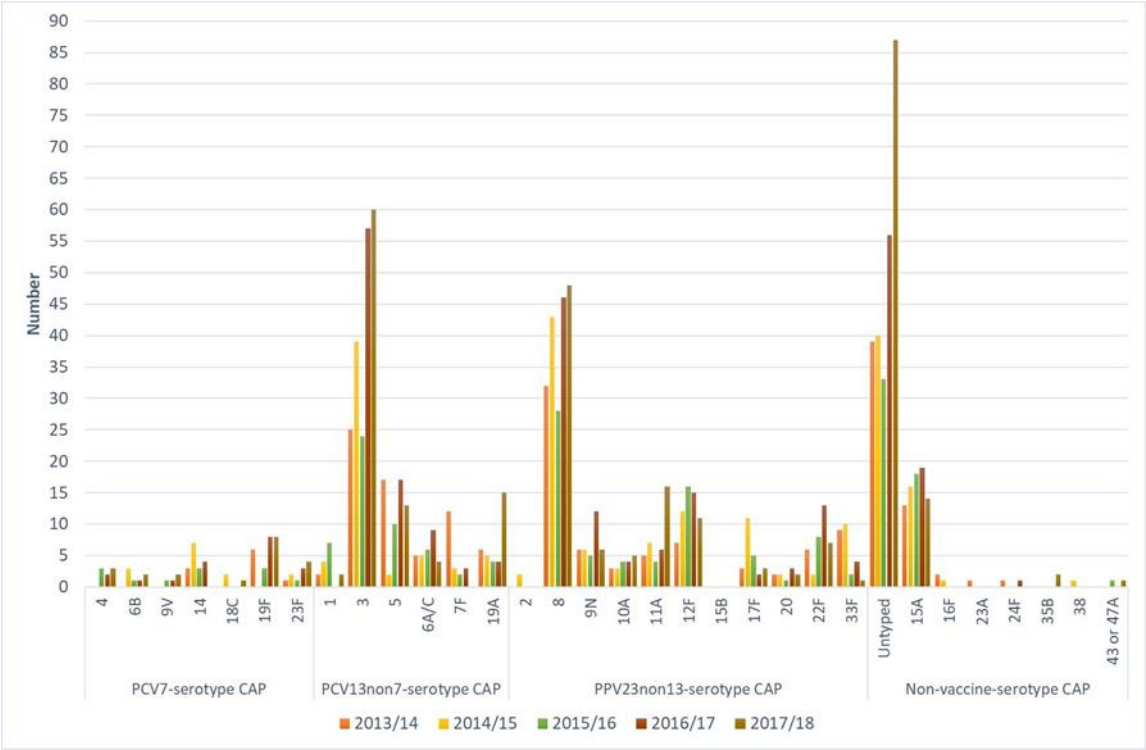


PCV7-serotype CAP: CAP due to serotypes included in PCV7; PCV13non7-serotype CAP: CAP due to serotypes included in PCV13, excluding serotypes also included in PCV7; PPV23non13-serotype CAP: CAP due to serotypes included in PPV23, excluding serotypes also included in PCV13; non-vaccine-serotype CAP: CAP due to a) any non-PCV13, non-PPV23 serotype and B) untyped pneumococcal cases—blood culture or Binax urinary antigen detection positive without subsequent serotype identification, or Bio-plex24 assay positive for cell wall polysaccharide only. CAP, community-acquired pneumonia; PCV, pneumococcal conjugate vaccine.

2.3.4; Pneumococcal serotypes

A total of 32 different serotypes were identified; 21 were definitively identified by Bio-plex24 or serum agglutination of bacteraemic cases while 11 were designated based on the predominant serotype derived from national IPD surveillance data (Figure 2.3 and Table 2.1). Of the 11 designated serotypes, nine matched the target serotypes, one was a different vaccine serotype (6A to 6C), and one was a NVT (15B to 15A). PCV7 serotypes were identified in 71 (6·6%) of the 1075 patients with pneumococcal CAP; serotype 19F was commonest (n=25, 33·3% of PCV7 serotypes), followed by serotype 14 (n=17, 22·7%) and 23F (n=11, 14·7%). PCV13non7 serotypes were identified in 349 (32·5%) patients, with serotype 3 being responsible for more than half of these cases (n=205, 56·9% of PCV13non7 serotypes).

Figure 2-3: Variation in absolute serotype number, grouped according to vaccine type, by study year among adults with pneumococcal CAP.



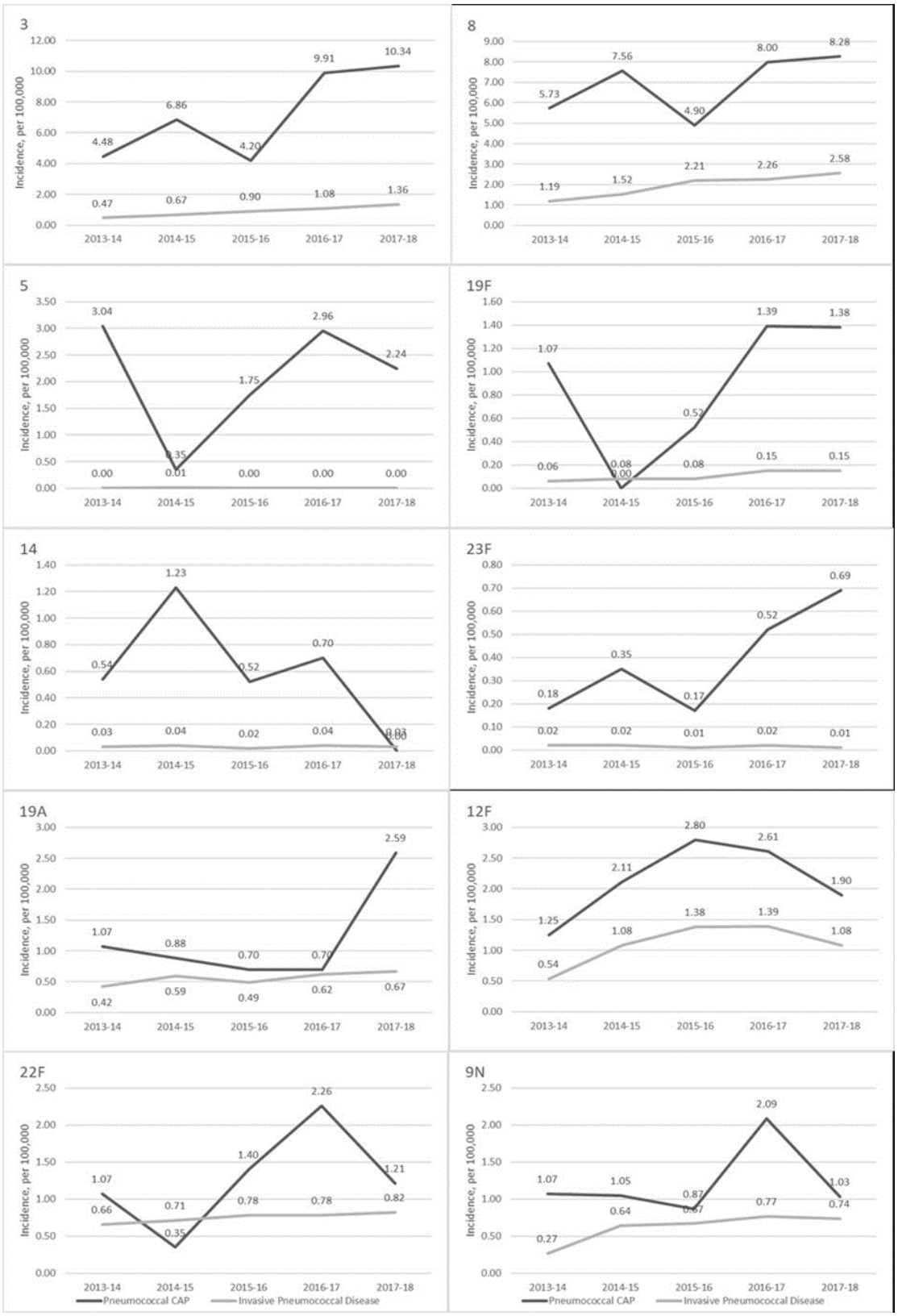
PCV7-serotype CAP: CAP due to serotypes included in PCV7; PCV13non7-serotype CAP: CAP due to serotypes included in PCV13, excluding serotypes also included in PCV7; PPV23non13-serotype CAP: CAP due to serotypes included in PPV23, excluding serotypes also included in PCV13; non-vaccine-serotype CAP: CAP due to a) any non-PCV13-serotype, non-PPV23-serotype and B) untyped pneumococcal cases—blood culture or Binax urinary antigen detection positive without subsequent serotype identification, or Bio-plex24 assay positive for cell wall polysaccharide only. CAP, community-acquired pneumonia; PCV, pneumococcal conjugate vaccine.

PPV23non13 serotypes were identified in 431 (40·1%) patients; serotype 8 was commonest (n=197, 44·1% of PPV23non7 serotypes) followed by serotypes 12F (n=60, 13·4%), 11A (n= 38, 8·5%), 22F (n=36, 8·1%) and 9N (n=35, 7·8%).

An NVT-serotype was identified in 321 (29·9%) patients, with serotype 15A identified in more than a quarter (n=80, 26·9% of NVT serotypes) while no serotype ('untyped' pneumococcal disease) was identified in 231 patients.

Compared to national IPD data over the same period, [37] proportions of serotype 3 disease were higher for CAP while PPV23non13-serotype disease was higher in IPD (Figure 2.4). The observed increase in serotype 3 pneumonia (annual IRR 1·28, 95% CI 1·24-1·32) was of similar magnitude to serotype 3 in IPD (annual IRR 1·23, 95% CI 1·12 – 1·36) (Table 2.4 and Figure2.5).

Figure 2-4: Overall trends in pneumococcal CAP and invasive pneumococcal disease incidence for individual serotypes between 2013 and 2018.



Incidence per 100 000 adult population. IPD, invasive pneumococcal disease; CAP, community-acquired pneumonia.

Table 2-4: Incident rate ratios for pneumococcal pneumonia cohort and IPD cohort between 2013 and 2018.

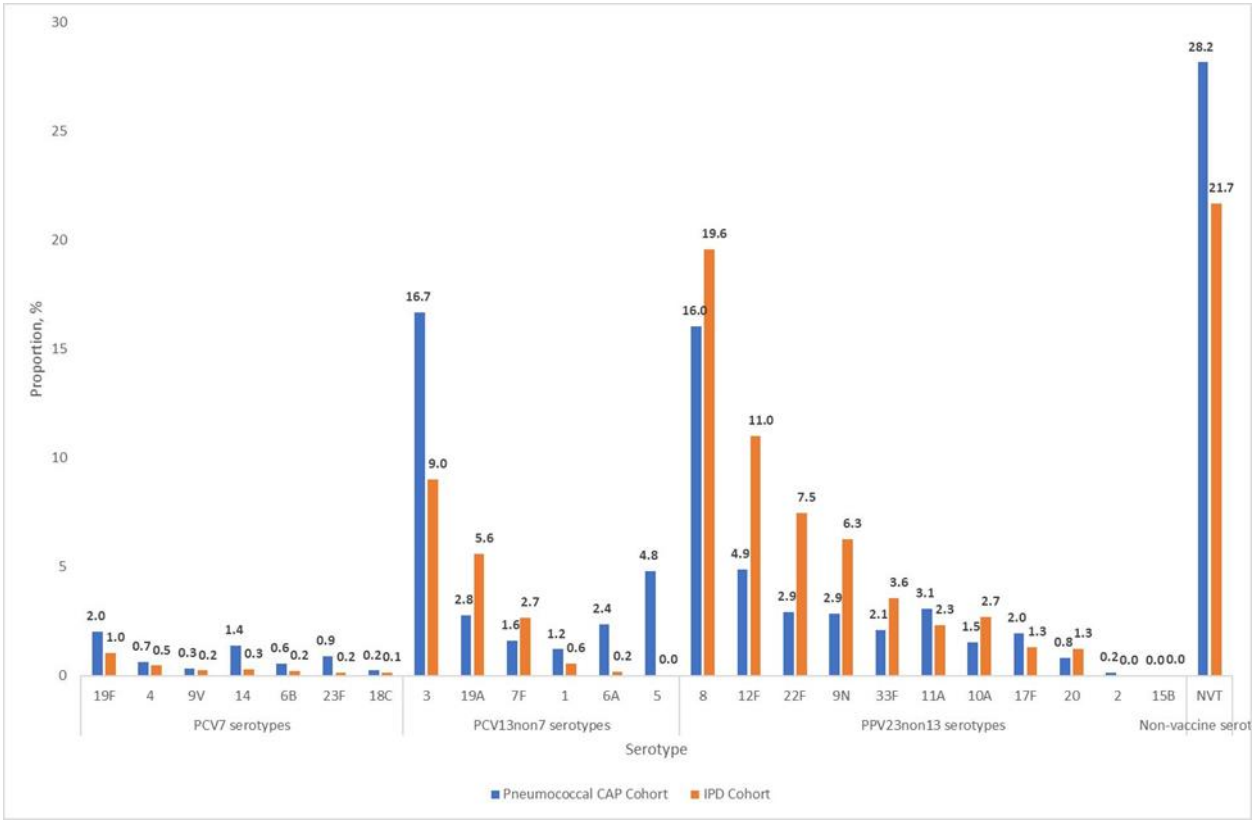
	2013-14 IRR	2014-15 IRR (95% CI)	2015-16 IRR (95% CI)	2016-17 IRR (95% CI)	2017-18 IRR (95% CI)	Change in IRR per year (95% CI)	p value for trend
National IPD cohort - serotype 3	1.0	1·42 (1·19-1·70)	1·91 (1·61-2·25)	2·27 (1·93-2·67)	2·87 (2·45-3·36)	1·28 (1·24-1·32)	**<0·001**
CAP cohort - serotype 3	1.0	1·53 (0·93-2·53)	0·94 (0·54-1·64)	2·21 (1·38-3·54)	2·31 (1·45-3·68)	1·23 (1·12-1·36)	**<0·001**
National IPD cohort - PCV7-serotype	1.0	1·12 (0·86-1·48)	1·09 (0·82-1·43)	1·26 (0·96-1·64)	1·35 (1·04-1·75)	1·07 (1·01-1·14)	**0·015**
CAP cohort - PCV7-serotype	1.0	1·37 (0·61-3·09)	1·17 (0·51-2·71)	1·65 (0·76-3·60)	1·73 (0·80-3·75)	1·13 (0·96-1·34)	0·135
National IPD cohort - PCV13non7-serotype	1.0	1·20 (1·08-1·33)	1·16 (1·04-1·29)	1·29 (1·17-1·43)	1·48 (1·34-1·64)	1·09 (1·07-1·11)	**<0·001**
CAP cohort - PCV13non7-serotype	1.0	0·86 (0·60-1·23)	0·78 (0·54-1·12)	1·35 (0·98-1·86)	1·35 (0·98-1·87)	1·12 (1·04-1·21)	**0·003**
National IPD cohort - PPV23non13-serotype	1.0	1·43 (1·34-1·53)	1·80 (1·69-1·91)	1·83 (1·72-1·95)	1·88 (1·77-2·00)	1·15 (1·13-1·16)	**<0·001**
CAP cohort - PPV23non13-serotype	1.0	1·29 (0·94-1·75)	1·00 (0·72-1·39)	1·35 (1·00-1·84)	1·29 (0·95-1·75)	1·06 (0·99-1·13)	0·112
National IPD cohort - Non-vaccine-serotype	1.0	1·12 (1·01-1·22)	1·05 (0·96-1·16)	1·16 (1·06-1·27)	1·32 (1·20-1·44)	1·06 (1·04-1·08)	**<0·001**
CAP cohort - Non-vaccine serotype	1.0	1·04 (0·65-1·65)	0·84 (0·51-1·36)	1·17 (0·74-1·82)	2·06 (1·38-3·08)	1·21 (1·10-1·33)	**<0·001**

Data are presented as incidence rate ratio (IRR) with 95% confidence intervals. IPD: invasive pneumococcal disease; CAP: Community-acquired pneumonia; PCV7-serotype: pneumococcal disease due to serotypes included in PCV7; PCV13non7- serotype: pneumococcal disease due to serotypes included in PCV13, excluding serotypes also included in PCV7; PPV23non13 -serotype: pneumococcal disease due to serotypes included in PPV23, excluding serotypes also included in PCV13;

CAP cohort: Non-vaccine-serotype: pneumococcal disease due to a) any non-PCV13-, non-PPV23- serotype and b) untyped pneumococcal cases – blood culture or BINAX UAD positive without subsequent serotype identification, or Bio-plex24 assay positive for cell wall polysaccharide only '

National IPD cohort: Non-vaccine-serotype: pneumococcal disease due to any non-PCV13-, non-PPV23-serotype case

Figure 2-5: Comparison of serotype proportions between pneumococcal pneumonia cohort and national invasive pneumococcal disease cohort between 2013 and 2018.



PCV7-serotype: pneumococcal disease due to serotypes included in PCV7; PCV13non7- serotype: pneumococcal disease due to serotypes included in PCV13, excluding serotypes also included in PCV7; PPV23non13-serotype: pneumococcal disease due to serotypes included in PPV23, excluding serotypes also included in PCV13; CAP cohort: non-vaccine-serotype: pneumococcal disease due to a) any non-PCV13-serotype, non-PPV23-serotype and b) untyped pneumococcal cases—blood culture or BINAX urinary antigen detection positive without subsequent serotype identification, or Bio-plex24 assay positive for cell wall polysaccharide only National IPD cohort: non-vaccine-serotype: pneumococcal disease due to any non-PCV13-serotype, non-PPV23-serotype case. CAP, community-acquired pneumonia; IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine.

2.3.5; Persons with PCV13-serotype pneumonia

Of 983 patients eligible for analysis (single serotype, or multiple serotypes not crossing vaccine serogroup classes), 325 had PCV13-serotype and 658 had non-PCV13-serotype disease (Table 2-5). Increasing age (per year increase, adjusted Odds Ratio (aOR) 1·02, 95% CI 1·01-1·03, p<0·001) and chronic kidney disease (aOR 1·71, 95% CI 1·02-2·86, p=0·019 respectively) were significantly associated with higher odds of PCV13-serotype disease compared to non-PCV13-serotype disease. Conversely, those living in residential care (aOR 0·28, 95% CI 0·10-0·75, p=0·012) or with active malignancy (aOR 0·52, 95% CI 0·31-0·90, p=0·019) had significantly lower odds of PCV13-serotype disease. On multivariable analysis, patients in the pneumococcal clinical risk group (aOR 1·73, 95% CI 1·31-2·28, p<0·001) and patients aged ≥65years with ≥1 risk factor (aOR 1·69, 95% CI 1·24-2·30, p=0·001) had significantly higher odds of PCV13-serotype whilst patients aged 16-64 years without risk factors had significantly lower odds of PCV13-serotype disease (aOR 0·59, 95% CI 0·43-0·81, P=0·001)(Table 2.6).

Table 2-5: Clinical features and comparative analysis of PCV13- versus non-PCV13-serotype CAP

	PCV13	Non-PCV13	OR (95%CI)	p value	aOR (95%CI)	p value
Patients	325	658				
Demographics						
Age, years	72·6 (62·1-82·2)	66·6 (50·3-78·6)		**<0·001**	1·02 (1·01-1·03)	**<0·001**
16-49 years	40 (12·3)	162 (24·6)	Reference			
50-64 years	66 (20·3)	145 (22·0)	1·84 (1·17-2·91)			
65-74 years	85 (26·2)	138 (21·0)	2·49 (1·59-3·91)			
75-84 years	75 (23·1)	129 (18·8)	2·35 (1·49-3·72)			
≥85 years	59 (18·2)	84 (12·8)	2·84 (1·73-4·66)	**<0·001**[#]		
Male	169 (52·0)	315 (47·9)	1·17 (0·90-1·53)	0·241		
Care Home Resident	5 (1·5)	24 (3·7)	0·41 (0·16-1·09)	0·066	0·28 (0·10-0·75)	**0·012**
PPV23 vaccination [a]	128 (42·0)	188 (28·6)	1·63 (1·22-2·17)	**<0·001**		
Comorbid disease						
Never smoker[#]	92 (29·2)	172 (26·9)	Reference			
Ex-smoker[#]	142 (45·1)	260 (40·7)	1·02 (0·74-1·41)			
Current smoker[#]	81 (25·7)	207 (32·4)	0·73 (0·51-1·05)	0·087#		
Alcohol excess	11 (3·4)	29 (4·4)	0·76 (0·37-1·54)	0·445	0.96 (0.46-1.99)	0.915
Malignancy	22 (6·8)	64 (9·7)	0·67 (0·40-1·11)	0·121	0·52 (0·31-0·90)	**0·019**
Liver disease	5 (1·5)	17 (2·6)	0·59 (0·22-1·61)	0·298	0.67 (0.24-1.89)	0.447
Kidney disease	35 (10·8)	38 (5·8)	1·97 (1·22-3·19)	**0·005**	1·71 (1·02-2·86)	**0·041**
Chronic heart disease	53 (16·3)	79 (12·0)	1·43 (0·98-2·08)	**0·063**	1.07 (0.72-1.60)	0.732
Congestive cardiac failure	24 (7·4)	33 (5·0)	1·51 (0·88-2·60)	0·135		
Ischaemic heart disease	35 (10·8)	55 (8·4)	1·32 (0·85-2·07)	0·218		
Chronic lung disease (excluding asthma)	98 (30·2)	170 (25·8)	1·24 (0·92-1·66)	0·153	1.04 (0.77-1.42)	0.782
COPD	84 (25·8)	155 (23·6)	1·13 (0·83-1·54)	0·431		
Asthma	30 (9·2)	79 (12·0)	0·75 (0·48-1·16)	0·193		
Diabetes Mellitus	49 (15·1)	96 (14·6)	1·04 (0·72-1·51)	0·84	0.90 (0.61-1.33)	0.601
Cerebrovascular disease	29 (8·9)	48 (7·3)	1·25 (0·77-2·02)	0·372	1.05 (0.63-1.74)	0.863
Cognitive impairment	8 (2·5)	24 (3·6)	0·67 (0·30-1·50)	0·325		
Immunocompromise	17 (5·2)	25 (3·8)	1·40 (0·74-2·63)	0·297	1.87 (0.95-3.70)	0.072

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TABLE 2.5: Clinical features and comparative analysis of PCV13- versus non-PCV13-serotype CAP (continued)

	PCV13	Non-PCV13	OR (95%CI)	p value	aOR (95%CI)	p value
Study Year						
6	60 (18·5)	107 (16·3)	Reference			
7	54 (16·6)	129 (19·6)	0·75 (0·48-1·17)			
8	47 (14·5)	104 (15·8)	0·81 (0·50-1·29)			
9	78 (24·0)	143 (21·7)	0·97 (0·64-1·48)			
10	86 (26·5)	175 (26·6)	0·88 (0·58-1·32)	0·952[#]		
Disease Severity						
CURB-65 0-1	117 (36·0)	330 (50·2)	Reference			
CURB-65 2	108 (33·2)	184 (28·0)	1·66 (1·20-2·28)			
CURB-65 ≥3	100 (30·8)	144 (21·9)	1·96 (1·40-2·74)	**<0·001**[#]		
Outcomes						
Critical Care admission	32 (9·8)	70 (10·6)	0·92 (0·59-1·43)	0·702		
30-day mortality	20 (6·2)	33 (5·0)	1·24 (0·70-2·20)	0·457		

Data are presented as n (%) or median (interquartile range). PPV23: 23-valent pneumococcal polysaccharide vaccine; COPD: chronic obstructive pulmonary disease; CURB-65: confusion, urea >7mmol.L-1, respiratory rate > 30 breaths.min-1, blood pressure <90mmHg [systolic] <60mmHg [diastolic], age ⩾65years. Odds ratio (OR) and p values compare PCV13 serotype disease to non-PCV13 serotype disease. aOR – adjusted for age, residential care status, active malignancy, liver disease, chronic alcohol excess, cerebrovascular disease, diabetes mellitus, chronic lung disease, chronic heart disease, immunosuppression, and chronic kidney disease. Bold values indicate p value <0.05. [a] – PPV23 vaccine status and smoking status unavailable for 67 and 29 patients respectively, # - p value for trend

Table 2-6: Association between clinical risk group and PCV13-serotype disease

	PCV13	Non-PCV13	OR (95% CI)	P value	aOR (95% CI)	P value
16-64 years, no clinical risk factor	72 (22·2)	208 (31·6)	0·62 (0·45-0·84)	**<0·001**	0·59 (0·43-0·81)	**0·001**
16-64 years, ≥1 risk factor	34 (10·4)	99 (15·1)	0·66 (0·44-0·99)	0·049	0·65 (0·43-0·98)	0·04
≥65 years, no clinical risk factor	75 (23·1)	137 (20·8)	1·14 (0·83-1·57)	0·419	1·14 (0·83-1·57)	0·422
≥65 years, ≥1 risk factor	144 (44·3)	214 (32·5)	1·65 (1·26-2·17)	**<0·001**	1·73 (1·31-2·28)	**<0·001**
Pneumococcal clinical risk group*	253 (77·8)	450 (68·4)	1·62 (1·19-2·21)	**0·002**	1·69 (1·24-2·30)	**0·001**
Number of risk factors						
0	147 (45·2)	345 (52·4)	Reference		Reference	
1	114 (35·1)	212 (32·2)	1·26 (0·94-1·70)		1·29 (0·96-1·74)	
2	46 (14·2)	81 (12·3)	1·33 (0·88-2·01)		1·40 (0·93-2·12)	
>3	18 (5·5)	20 (3·0)	2·11 (1·08-4·12)	**0·013#**	2·14 (1·10-4·18)	0·056#

Data are presented as n (%). Adjusted OR are corrected for residential care status. Bold values indicate p value <0.05. Clinical risk factors include; chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease, immunosuppression (splenic dysfunction, haematological disease including malignancy, solid organ or bone-marrow transplant, immunodeficiency, HIV, or treatment with immunosuppressive therapies but not steroids), diabetes mellitus requiring therapy, splenic dysfunction, and individuals with cerebrospinal fluid (CSF) leaks or cochlear implants.

**: age ⩾65years or age 16-64years with ⩾1 risk factor, #: p value for trend*

Sensitivity analysis excluding all cases with designated serotypes (n=157) did not significantly alter findings. Conversely, none of the described associations remained significant when all serotype 3 cases were excluded (Table 2.7)

Table 2-7: Sensitivity analysis examining the clinical features of those with PCV13- versus non-PCV13-serotype CAP, excluding serotype 3.

	PCV13	Non-PCV13	OR (95% CI)	P value
16-64 years, no clinical risk factor	35 (23.3)	208 (31·6)	0.81 (0.52-1.29)	0.38
16-64 years, ≥1 risk factor	24 (16.0)	99 (15·1)	1.16 (0.70-1.91)	0.573
≥65 years, no clinical risk factor	32 (21.3)	137 (20·8)	0.89 (0.56-1.43)	0.641
≥65 years, ≥1 risk factor	59 (39.3)	214 (32·5)	1.17 (0.78-1.77)	0.438
Pneumococcal clinical risk group*	115 (76.7)	450 (68·4)	1.23 (0.77-1.94)	0.38
Number of risk factors				
0	67 (44.7)	345 (52·4)	Reference	
1	58 (38.7)	212 (32·2)	1.30 (0.86-1.98)	
2	21 (14.0)	81 (12·3)	1.24 (0.69-2.22)	
>3	4 (2.7)	20 (3·0)	0.79 (0.22-2.78)	0.576

Data are presented as n (%). Bold values indicate p value <0.05. Clinical risk factors include; chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease, immunosuppression (splenic dysfunction, haematological disease including malignancy, solid organ or bone-marrow transplant, immunodeficiency, HIV, or treatment with immunosuppressive therapies but not steroids), diabetes mellitus requiring therapy, splenic dysfunction, and individuals with cerebrospinal fluid (CSF) leaks or cochlear implants.

**: age ⩾65years or age 16-64years with ⩾1 risk factor, #: p value for trend*

2.3.6; Persons with PPV23 serotype pneumonia

Of 1048 patients eligible for analysis (single serotype, or multiple serotypes not crossing vaccine serogroup classes), 732 had PPV23-serotype and 316 had non-PPV23-serotype disease (Table 2.8). There were no significant associations between risk of PPV23 serotype disease and individual co-morbidities identified in the multivariable analysis. On multivariable analysis of clinical risk and PPV23 serotype disease, both the pneumococcal clinical risk group (aOR 0·65, 95% CI 0·48-0·88, p=0·006) and patients 16-64 years with ≥1 risk factor (aOR 0·51, 95% CI 0·35-0·73, p<0·001) had significantly lower odds of PPV23-serotype disease (Table 2.9). Patients 16-64 years without risk factors had significantly higher odds of PPV23-serotype disease (aOR 1·54. 95% CI 1·13-2·10, p=0·006).

Table 2-8: Clinical features and comparative analysis of those with PPV23- versus non-PPV23-serotype CAP

	PPV23	Non-PPV23	OR (95%CI)	p value	aOR (95%CI)	p value
Patients	732	316				
Demographics						
Age, years (IQR)	69·3 (54·2-80·1)	69·1 (53·1-80·6)		0·953	1·00 (0·99-1·01)	0·761
16-49 years	149 (20·4)	62 (19·6)	Reference			
50-64 years	153 (20·9)	69 (21·8)	0·92 (0·61-1·39)			
65-74 years	169 (23·1)	68 (21·5)	1·03 (0·69-1·56)			
75-84 years	156 (21·3)	65 (20·6)	0·99 (1·66-1·51)			
≥85 years	105 (14·3)	52 (16·5)	0·84 (0·54-1·31)	0·658[#]		
Male	346 (47·4)	156 (49·4)	0·92 (0·71-1·20)	0·558		
Care Home Resident	23 (3·2)	11 (3·5)	0·90 (0·43-1·88)	0·785	0.86 (0.41-1.82)	0.701
PPV23 vaccination [a]	236 (34·5)	105 (36·5)	0·92 (0·69-1·22)	0·55		
Comorbid disease						
Smoking status [a]						
Never smoker	199 (28·2)	87 (27·9)	Reference			
Ex-smoker	298 (42·3)	129 (41·4)	1·01 (0·73-1·40)			
Current smoker	208 (29·5)	96 (30·8)	0·95 (0·67-1·34)	0·756		
Alcohol excess	26 (3·6)	15 (4·8)	0·74 (0·39-1·42)	0·36	0.76 (0.39-1.49)	0.419
Malignancy	55 (7·5)	35 (11·1)	0·65 (0·42-1·02)	0·06	0·63 (0·40-1.02)	0·058
Liver disease	15 (2·1)	8 (2·5)	0·81 (0·34-1·92)	0·625	0.85 (0.35-2.10)	0.729
Kidney disease	62 (8·5)	18 (5·7)	1·53 (0·89-2·64)	0·121	1.63 (0.93-2.88)	0.090
Chronic heart disease	90 (12·3)	49 (15·5)	0·76 (0·52-1·11)	0·16	0.71 (0.48-1.05)	0.086
Congestive cardiac failure	36 (4·9)	25 (7·9)	0·60 (0·35-1·02)	0·058		
Ischaemic heart disease	67 (9·2)	30 (9·5)	0·96 (0·61-1·51)	0·861		
Chronic lung disease (excluding asthma)	194 (26·5)	73 (31·5)	0·79 (0·57-1·08)	0·141	0.95 (0.70-1.30)	0.770
COPD	172 (23·5)	80 (25·3)	0·91 (0·67-1·23)	0·527		

Table 2-8: Clinical features and comparative analysis of those with PPV23- versus non-PPV23-serotype CAP (continued)

	PPV23	Non-PPV23	OR (95%CI)	p value	aOR (95%CI)	p value
Asthma	87 (11·9)	33 (10·4)	1·16 (0·76-1·77)	0·501		
Diabetes Mellitus	111 (16·2)	47 (14·9)	1·02 (0·71-1·48)	0·904	0.99 (0.68-1.45)	0.958
Cerebrovascular disease	55 (7·5)	25 (7·9)	0·95 (0·58-1·55)	0·824	0.92 (0.55-1.53)	0.742
Cognitive impairment	24 (3·3)	11 (3·5)	0·94 (0·45-1·94)	0·867		
Immunocompromise	30 (4·1)	15 (4·8)	0·86 (0·45-1·62)	0·635	0.97 (0.50-1.90)	0.937
Disease Severity						
CURB65 0-1	316 (43·2)	155 (49·1)	Reference			
CURB65 2	225 (30·7)	87 (27·5)	1·27 (0·93-1·74)			
CURB65 ≥3	191 (26·1)	74 (23·4)	1·27 (0·91-1·76)	0·119#		
Study Year						
6	126 (17·2)	50 (15·8)	Reference			
7	142 (19·4)	56 (17·7)	1·00 (0·64-1·58)			
8	113 (15·4)	45 (14·2)	1·00 (0·62-1·61)			
9	172 (23·5)	67 (21·2)	1·02 (0·66-1·57)			
10	179 (24·5)	98 (31·0)	0·72 (0·48-1·09)	0·117#		
Outcomes						
Critical Care admission	73 (10·0)	33 (10·4)	0·95 (0·62-1·47)	0·817		
30-day mortality	44 (6·0)	10 (3·2)	1·96 (0·97-3·95)	0·056		

Data are presented as n (%) or median (interquartile range). PPV23: 23-valent pneumococcal polysaccharide vaccine; COPD: chronic obstructive pulmonary disease; CURB-65: confusion, urea >7mmol.L-1, respiratory rate > 30 breaths.min-1, blood pressure <90mmHg [systolic] <60mmHg [diastolic], age ⩾65years. Odds ratio (OR) and p values compare PPV23 serotype disease to non-PPV23 serotype disease. . aOR – adjusted for age, residential care status, active malignancy, liver disease, chronic alcohol excess, cerebrovascular disease, diabetes mellitus, chronic lung disease, chronic heart disease, immunosuppression, and chronic kidney disease. Bold values indicate p value <0.05. [a] – PPV23 vaccine status and smoking status unavailable for 68 and 29 patients respectively, # - p value for trend

Table 2-9: Association between clinical risk group and PPV23-serotype disease

	PPV23	Non-PPV23	OR (95% CI)	P value	aOR (95% CI)	P value
16-64 years, no clinical risk factor	223 (30·5)	70 (22·1)	1·54 (1·13-2·10)	**0·006**	1·54 (1·13-2·10)	**0·006**
16-64 years, ≥1 risk factor	79 (10·8)	61 (19·3)	0·51 (0·35-0·73)	**<0·001**	0·51 (0·35-0·73)	**<0·001**
≥65 years, no clinical risk factor	160 (21·9)	70 (22·2)	0·98 (0·72-1·35)	0·916	0·98 (0·72-1·35)	0·706
≥65 years, ≥1 risk factor	270 (36·9)	115 (36·4)	1·02 (0·78-1·34)	0·879	1·02 (0·78-1·34)	0·685
Pneumococcal clinical risk group*	509 (69·5)	246 (77·9)	0·65 (0·48-0·88)	**0·006**	0·65 (0·48-0·88)	**0·006**
Number of risk factors						
0	383 (52·3)	140 (44·3)	Reference		Reference	
1	221 (30·2)	129 (40·8)	0·63 (0·47-0·84)		0·63 (0·47-0·84)	
2	95 (13·0)	41 (13·0)	0·85 (0·56-1·28)		0·85 (0·56-1·28)	
>3	33 (4·5)	6 (1·9)	2·01 (0·82-4·91)	0·617[#]	2·01 (0·82-4·91)	**0·002[#]**

Data are presented as n (%). Bold values indicate p value <0.05. Clinical risk factors include; chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease, immunosuppression (splenic dysfunction, haematological disease including malignancy, solid organ or bone-marrow transplant, immunodeficiency, HIV, or treatment with immunosuppressive therapies but not steroids), diabetes mellitus requiring therapy, splenic dysfunction, and individuals with cerebrospinal fluid (CSF) leaks or cochlear implants.

**: age ⩾65years or age 16-64years with ⩾1 risk factor, #: p value for trend*

Sensitivity analyses excluding 1) all cases with designated serotypes (n=183) and 2) all cases of serotype 3, from the model did not significantly alter findings (Table 2.10).

An exploratory analysis to identify persons at risk of PPV23non13-serotype disease found that patients aged 16-64 years without risk factors had significantly higher odds of PPV23non13-serotype disease (aOR 1·94, 95% CI 1·42-2·65, p<0·001), whilst patients aged ≥65 years with ≥1 risk factor (aOR 0·69, 95% CI 0·51-0·94, p=0·017) and pneumococcal clinical risk group (aOR 0·52, 95% CI 0·38-0·70, p<0·001) had significantly lower odds of PPV23non13-serotype disease compared to non-PPV23non13-serotype disease.

Table 2-10: Sensitivity analysis examining the clinical features of those with PPV23- versus non-PPV23-serotype CAP, excluding serotype 3.

	PPV23	Non-PPV23	OR (95% CI)	P value
16-64 years, no clinical risk factor	182 (34.3)	70 (22·1)	1.83 (1.33-2.52)	**<0.001**
16-64 years, ≥1 risk factor	68 (12.8)	61 (19·3)	0.61 (0.42-0.90)	**0.011**
≥65 years, no clinical risk factor	105 (19.8)	70 (22·2)	0.87 (0.62-1.22)	0.409
≥65 years, ≥1 risk factor	176 (33.2)	115 (36·4)	0.87 (0.65-1.16)	0.336
Pneumococcal clinical risk group*	349 (65.7)	246 (77·9)	0.55 (0.40-0.75)	**<0.001**
Number of risk factors				
0	287 (54.1)	140 (44·3)	Reference	
1	158 (29.8)	129 (40·8)	0.60 (0.44-0.81)	
2	61 (12.6)	41 (13·0)	0.80 (0.51-1.24)	
>3	19 (3.6)	6 (1·9)	1.54 (0.60-3.65)	**0.005**

Data are presented as n (%). Bold values indicate p value <0.05. Clinical risk factors include; chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease, immunosuppression (splenic dysfunction, haematological disease including malignancy, solid organ or bone-marrow transplant, immunodeficiency, HIV, or treatment with immunosuppressive therapies but not steroids), diabetes mellitus requiring therapy, splenic dysfunction, and individuals with cerebrospinal fluid (CSF) leaks or cochlear implants.

**: age ⩾65years or age 16-64years with ⩾1 risk factor, #: p value for trend*

2.4; Discussion

2.4.1; Summary of key findings

The key study findings are 1) the annual incidence of adult pneumococcal CAP has increased from 32·2 per 100,000 population in 2013 to 48·2 per 100,000 population in 2018, concurrent with increases in the incidence of overall CAP, 2) this increase is predominantly due to increases in PCV13non7- and NVT-serotype pneumonia, 3) serotype 3 accounts for more than half of PCV13non7-serotype pneumonia, 4) PCV13-serotype pneumonia is 73% more likely in patients in pneumococcal clinical risk group, while 5) PPV23-serotype pneumonia is 54% more likely in younger patients who are not in the pneumococcal clinical risk group.

The epidemiology of adult pneumococcal pneumonia in Europe appears to be diverging from that seen in the US. Evidence of pneumococcal infection was present in more than a third of adults hospitalised with CAP, consistent with other recent reports from Europe.[70,71] In contrast, in the US, *Streptococcus pneumoniae* has recently been implicated in 8 - 12% of hospitalised cases of CAP.[7,72] During 2008-2013, there were early indications of a decline in CAP due to PCV13 serotypes in adults following PCV7 substitution with PCV13 in the childhood immunisation programme. However, these latest findings in a previously untested and unreported cohort of patients from Nottingham indicate that PCV13 serotypes continue to account for a large proportion (40·6%) of adult CAP, with serotype 3 alone comprising 47·1% of PCV13 serotype cases. Pneumococcal carriage studies[73,74] and national surveillance of IPD[38] have also observed a limited direct and indirect effect of PCV13 vaccination on serotype 3.

These results are consistent with data indicating the serotype 3 antigen within PCV13 may provide suboptimal direct and indirect protection.[75] Notwithstanding serotype 3, there appears to be a persistence of PCV13 serotypes causing CAP. Serotypes 3, 5 and 6A were relatively more common in CAP compared to IPD, possibly indicating a predilection for pneumonia (rather than IPD) with these serotypes, as also observed by others.[76,77]

This study identified multiple serotypes in 10.9% of patients with pneumococcal pneumonia. This is higher than the proportion with multiple serotypes identified in IPD cohorts. The relevance and implications of this finding warrants further investigation.

Based on data from 2008 – 2013, it was previously reported that PCV13-serotype CAP was *less* common in adults in the pneumococcal clinical risk group compared to adults aged 16 – 64 years without clinical risk factors.[78] Those data reflected the situation within the first few years after introduction of the childhood PCV13 immunisation programme. Since then, the burden of PCV13-serotype CAP has shifted and adults in pneumococcal clinical risk group are at increased risk of infection. This association is dominated by serotype 3 which may reflect the invasiveness potential of this serotype, its penchant for pneumonia (compared to IPD) and its persistent carriage amongst children and adults. The influence of the recently emerged Clade II lineage (of serotype 3) in relation to clinical disease presentation is unclear.[79,80]

A large proportion of pneumococcal CAP was due to PPV23non13-serotype pneumonia (40·2%) with no significant change in incidence during 2013-2018.

Serotype 8 was commonest, similar to national IPD trends.[37] Although carriage of serotype 8 in children is rare, colonisation in young adults has been observed and may represent the reservoir from which adult pneumococcal infections arise.[81] In England and Wales, uptake of PPV23 vaccination in older adults and pneumococcal clinical risk groups has remained stable (~70%) over the study period.[82] The lack of significant change in the incidence of PPV23non13-serotype pneumonia suggests the replacing serotypes in pneumococcal pneumonia are predominantly NVT serotypes covered by neither PCV13 nor PPV23 vaccines. This is consistent with the observed increase in incidence of NVT-serotype pneumococcal pneumonia both in this study, and in other cohorts.[37,41]

It was observed that the odds of PPV23-serotype CAP were *higher* in patients *outside* the pneumococcal clinical risk group, specifically in patients aged 16-64 years without risk factors (aOR 1·54), but lower in patients in the pneumococcal clinical risk group (aOR 0·61). These associations were amplified when the analyses were restricted to patients with PPV23non13-serotype pneumonia (aOR 2·39 and aOR 0·42) and could reflect individual direct protection offered by PPV in 'at-risk' adults.[83]

2.4.2; Strengths and limitations

This large prospective population-based cohort study describes trends in pneumococcal serotypes implicated in adult pneumococcal pneumonia over the last five years, during which PCV13 replaced PCV7 in the national childhood immunisation programme. Unlike laboratory-based studies, our study population is not over-represented by patients with chronic lung disease or

those requiring invasive respiratory procedures.[77] Use of the novel Bio-plex24 assay enabled identification of PCV13 and PPV23 serotypes in patients presenting with non-invasive disease, which is the vast majority of adults with CAP, compared with previous studies which have been unable to identify PPV23-non13-serotype disease from non-invasive samples and have classified these cases as non-vaccine-type infection only.

An increase in incidence of all-cause CAP and pneumococcal CAP was observed over a 5-year period which we have interpreted as representing a true increase in disease burden. The possibility that some of this increase may have been due to healthcare system changes resulting in a shift from primary to secondary care management for CAP cannot be excluded. However, the lack of any substantial change over time in the distribution of low versus high severity pneumonia on admission suggests this is unlikely to be a major factor.

One limitation of this study relates to cross-reactivity of the Bio-plex24 assay. Non-specific cross-reactivity for serotypes 7F, 18C, 20 and 22F was noted during testing of samples from September 2014 to August 2015. The reported results are likely to be conservative, accepting some under-representation of serotypes 7F, 18C, 19F, 20, and 22F for that year. Following modifications to the assay, this non-specific cross-reactivity did not affect results for the other 4 years. For 11 serotypes displaying cross-reactivity with other serotypes not targeted by the Bio-plex24 assay designated cases to a single serotype based on the predominant serotype derived from national IPD data. A consequence of this methodology is the potential under-representation of less frequent serotypes. In

sensitivity analyses investigating the influence of the method of serotype designation on results, no major differences were detected (supplementary data available on request). Any overall under-representation of NVT serotypes arising from serotype designation would mean that our reported finding of an increased incidence of NVT-serotype CAP is conservative.

Secondly, all untyped pneumococcal isolates were considered NVT serotypes, potentially leading to an over-representation of NVT-serotype CAP. The impact of this on the overall findings is likely to be small given the high sensitivities of the serotyping methods used.

Additionally, as this study was performed in one geographical area, the serotype trends observed may have been due to local/regional epidemiological changes and our findings may not be applicable to other populations. Nevertheless, the main findings are consistent with trends observed from national IPD data.

2.4.3; Implications

An increase in pneumococcal CAP is reported, predominantly due to increases in NVT serotypes and serotype 3. Pneumococcal vaccines targeting emerging serotypes are needed.

Chapter 3: Experiences, concerns, and needs in recovery from Community-Acquired Pneumonia – a qualitative interview study of patients and healthcare professionals

3.1; Introduction

Between 0.5 and 1% of adults in the UK will develop Community-Acquired Pneumonia (CAP) annually,[84] corresponding to over 100,000 hospital admissions in England and Wales.[85] The average length of hospital stay is 6 days.[3] However, following hospital discharge, patients continue to experience substantial morbidity; at 4 weeks post-discharge 70% of patients report the presence of 1 or more symptom and up to 50% fail to return to normal activities of daily living or occupation.[86] Healthcare utilisation is high with 40%-60% of patients re-consulting health services within 4 weeks of discharge, including hospital readmission rate of 10%.[87]

Despite the high morbidity of disease extending over several weeks, most research into CAP has focussed primarily on the initial diagnosis and management of CAP. By contrast, studies of recovery from CAP are limited and lack consensus regarding what constitutes 'normal recovery.'[86] Moreover, very little is known about what patients experience during recovery from CAP, their wants and needs, nor what healthcare providers themselves understand regarding recovery from CAP.

Patient-centred care and empowerment has been recommended by national and international guidance as an important approach to improve outcomes, increase satisfaction, and reduce morbidity across a wide variety of diseases.[88-90] The aim of this study was to explore patient and healthcare professional knowledge, experiences, and expectations regarding recovery following hospitalisation with an episode of CAP.

3.2; Methods

3.2.1; Patient and public involvement

Patient and public involvement (PPI) was employed during the design of the study. Ten individuals with personal experience of CAP, who were members of the Nottingham Respiratory Infection research PPI group, contributed to protocol development and piloted the patient interview script, informing subsequent iterations.

3.2.2; Study design

This qualitative study was nested within a large prospective cohort study of adults hospitalised with CAP between June 2017 and January 2019 at two large teaching hospitals in UK, collectively covering the catchment area for acute and emergency admissions in Greater Nottingham. The Standards for Reporting Qualitative Research (SRQR) guideline was adopted.[91] Study procedures were research ethics by South West – Frenchay Research Ethics Committee (17/SW/0087) (Appendix 3).

3.2.3; Patient recruitment

The study aimed to recruit a diverse group of patients (variation across age, sex, and CAP severity) employing convenience sampling rather than recruiting consecutive CAP admissions. Eligible patients were adults (≥16 years) with a clinical diagnosis of CAP defined as: the presence of one or more symptoms of acute lower respiratory tract infection (cough, increasing breathlessness, sputum production, chest pain, and fever); evidence of acute infiltrates consistent with a respiratory infection on admission plain chest radiograph; and treated by the

clinical team for CAP. Exclusion criteria included; inability to understand verbal or written information in English, hospital admission within preceding 10 days, active tuberculosis, post-obstructive pneumonia secondary to lung cancer, aspiration pneumonia, inability to provide informed consent, or patients who were unable to comply with follow-up interviews post-discharge. Written informed consent was obtained from all participants.

To enable capture of temporal changes in symptoms, interviews were conducted at 2 weeks (initial), 6-8 weeks (interim) and 14 weeks (final) post-discharge. The initial interview was conducted in the participant's home. Verbal conformation of continued consent was obtained for subsequent interviews which were conducted either by telephone or in the participant's home dependent on participant preference.

3.2.3; Healthcare professional recruitment

Healthcare professionals (HCPs) on acute medical wards across the same two teaching hospitals caring for adults admitted with CAP were approached by study researchers regarding study participation. Following informed consent, HCP participants proceeded to complete a single semi-structured interview via telephone or in person. Through a combination of purposeful and snowball sampling, the study cohort comprised a broad range of professions (registered nurses, occupational therapists, physiotherapists, discharge co-ordinators, and doctors) and grades of seniority.

3.2.4; Data collection and analysis

Qualitative data for the patient group was collected from June 2017 to April 2018 and for the HCP group between September 2017 and January 2019. Semi-structured interviews were conducted by three researchers (DA female, HJP male, CST male) using a pre-designed interview script to ensure each pre-defined topic was discussed whilst permitting extended participant-directed discussion. Patient interviews were repeated at three time points in recovery to capture longitudinal changes in symptoms, functional ability, and overall experience. Pre-defined topics for discussion in the respective interviews are outlined in table 3.1.

Interviews were digitally audio-recorded and transcribed verbatim by a specialist transcription company. Transcripts were checked for accuracy by two researchers (DA & HJP), with all transcripts annotated to anonymize and de-identify participants. Each interview was coded as soon as possible to allow for the development of new concepts that were subsequently incorporated into the interview schedule, allowing these to be explored at later interviews. Each new concept was provisional unless it was repeatedly found to be present in each interview.

Data were interpreted inductively following Braun and Clarke's phases of thematic analysis.[92] Transcripts were coded independently by two researchers (DA and HJP). Coding decisions were reviewed, compared, and discussed until themes were agreed. A third researcher (MB) reviewed the generated themes. This challenged, complemented, and informed the developing analysis. An electronic database of codes and data excerpts were compiled using Microsoft

Word© and these were revised during the iterative process. Themes are presented with verbatim quotes in italics.

Table 3-1: pre-defined topics for discussion at semi-structured interview

Healthcare professional interviews	Patient interviews
Current practice in pneumonia recovery	Pneumonia diagnosis
Satisfaction with current approach	Hospital admission for pneumonia
Experience of patient re-consultation	Pneumonia recovery following discharge
Approaches to improving patient care	Impact of pneumonia on activity / function

3.3; Results

3.3.1; Participant Characteristics

3.3.1.1; Patient participants

Of 204 eligible patients, 18 were approached to participate, with 16 consenting to study enrolment. One participant withdrew due to an emergency hospital admission. Eight (53.3%) participants were female, and mean age of participants was 53 years (±15.22). Fourteen participants completed all interviews; one did not complete the final interview. Patient-reported symptoms during recovery from CAP are detailed in Table 3.2.

Nine (60%) participants re-consulted their General Practitioners (GPs) before the initial interview at 14 days. Reasons for re-consultation included; seeking reassurance regarding course of recovery, advice on health promotion and lifestyle modification, and prevention of recurrence. Five (33%) patients reported persistent symptoms at 14-weeks.

3.3.1.2; Healthcare professional participants

Twenty-nine healthcare professionals were enrolled and completed interviews; ten junior doctors (foundation year 1 to specialist trainee 5), ten allied healthcare professionals (three staff nurses, two junior sisters, one discharge co-ordinator, two physiotherapists, an advanced nurse practitioner, and a senior sister), and nine Consultants; respiratory medicine (n=4), acute medicine (n=3), health care of the elderly (n=2).

Table 3-2: Symptoms reported by patients during recovery from CAP

Participant	Age	Gender	*CURB-65 Score*	Admission Symptoms	Hospital Inpatient stay (days)	Week 2 Symptoms	Re-consultation	Week 6-8 Symptoms	Re-consultation	Week 14 Symptoms
1	74	Female	***1***	Cough, Dyspnoea, Chest Pain, Pyrexia, Fatigue, Musculoskeletal pain, Headache	5	Dyspnoea, Fatigue, Musculoskeletal pain, Cognitive impairment	NO	Fatigue	Consultant	NIL
2	31	Male	0	Cough, Chest pain, Musculoskeletal pain	4	Cough, Chest Pain	NO	Cough, Chest Pain, Dyspnoea, Fatigue	GP / Consultant	Cough SOB
3	67	Female	***1***	Cough, Dyspnoea, Fall	4	Cough, Dyspnoea, Fatigue	GP	Dyspnoea	GP	NIL
4	73	Male	***1***	Cough, Haemoptysis, Pyrexia, Headache	10	Cough, dyspnoea	NO	Cough, dyspnoea	NO	NIL
5	41	Female	1	Cough, dyspnoea, Chest pain, Pyrexia, Headache, Fatigue	4	Cough, dyspnoea, Fatigue, Cognitive	GP	Dyspnoea, Fatigue	GP / Consultant	NIL

Participant	Age	Gender	*CURB-65 Score*	Admission Symptoms	Hospital Inpatient stay (days)	Week 2 Symptoms	Re-consultation	Week 6-8 Symptoms	Re-consultation	Week 14 Symptoms
6	31	Female	1	Cough, dyspnoea, Pyrexia	4	Dyspnoea, Fatigue, Cognitive impairment, Musculoskeletal pain	GP (Antibiotics)	NIL	Consultant	NIL
7	55	Female	0	Chest pain	2	Dyspnoea, Fatigue	GP	Nil	Consultant	Nil
8	49	Male	1	Coryzal, Cough, dyspnoea, Chest pain, Pyrexia, Nausea, Musculoskeletal pain	5	Cough, Dyspnoea, Fatigue, Musculoskeletal pain, Dizziness	GP	Cough, dyspnoea, Fatigue, Cognitive impairment	In Hospital Antibiotics (LRTI)	Cough, Dyspnoea, Fatigue, Dyspepsia,
9	60	Female	1	Cough, dyspnoea, Fatigue	7	Dyspnoea, Fatigue, cognitive	GP	Dyspnoea, fatigue	GP / Consultant	Dyspnoea, Fatigue
10	50	Female	1	Dyspnoea, Fatigue, Sore throat, Cough, musculoskeletal pain	5	Dyspnoea, Fatigue, Cognitive	GP	Nil	GP / GP	Nil

Participant	Age	Gender	*CURB-65 Score*	Admission Symptoms	Hospital Inpatient stay (days)	Week 2 Symptoms	Re-consultation	Week 6-8 Symptoms	Re-consultation	Week 14 Symptoms
11	64	Male	0	Cough, Chest pain, Pyrexia, Fatigue, Dyspepsia	3	Cough Fatigue	NO	Nil	NO	Nil
12	53	Male	0	Coryzal, dyspnoea	4	Cough, Dyspnoea, Fatigue, Unsteady, Cognitive impairment	NO	Nil	NO	Fatigue
13	40	Male	0	Dyspnoea, wheeze	7	Dyspnoea Fatigue, Anxiety	GP	Nil	NO	Nil
14	43	Male	2	Chest pain, Pyrexia, Fatigue	3	Cough, Chest pain, Fatigue	NO	Nil	NO	Nil
15	81	Female	***2***	Cough, Chest pain, fatigue	8	Cough, Dyspnoea, Fatigue, Chest pain	GP	Dyspnoea, Fatigue, Back pain	Consultant	SOB

Participant	Age	Gender	*CURB-65 Score*	Admission Symptoms	Hospital Inpatient stay (days)	Week 2 Symptoms	Re-consultation	Week 6-8 Symptoms	Re-consultation	Week 14 Symptoms

3.3.2; Themes

Three themes with corresponding sub-themes were identified: 1) Attitudes to CAP and recovery; 2) Re-consultation and 3) Support during CAP recovery (Table 3.2).

Table 3-3: Main themes and sub-themes identified

Theme 1: Attitudes to CAP and recovery	Theme 2: Re-consultation	Theme 3: Support during CAP recovery
Subtheme 1.1: CAP diagnosis	**Subtheme 2.1:** Recurrence of CAP and reconsultation	**Subtheme 3.1**: Provision of Information
Subtheme 1.2: Expectations of CAP recovery		**Subtheme 3.2:** Post-discharge follow-up
Subtheme 1.3: Patient vulnerability		

3.3.2.1; Theme 1: Attitudes to CAP and recovery

Patients commonly reported friends or family members having had prior experience of CAP. When personally faced with a diagnosis of "pneumonia", patients described significant anxiety and worry especially regarding associated morbidity and mortality. *"… I'm 73, has this done anything to cut short whatever might have been?"* (Patient 4, interview 1). This anxiety was recognised by HCPs as frightening for some, such as the elderly. *'… there's still a perception out there that pneumonia is something that the grim reaper brings'* (HCP 10, Junior Doctor).

Despite this anxiety, many patients described an expectation that recovery following an episode of CAP would be prompt, with full recovery coinciding with completion of antibiotic therapy, like their previous experiences of 'chest infections or infective exacerbations of co-morbid diseases. Over the course of interviews, many patients continued to be surprised by the slowness of their recovery; "*…this has taken two or three weeks and it's just go slow*". (Patient 14, interview 1), *"it is nothing like you think it's going to be, it's nothing like an infection previously, it goes on forever!"* (Patient 6, interview 2). Some patients reported that their family or colleagues also expected recovery to be more straightforward leading patients to sense a lack of understanding on their part.

Most HCPs recognised that the patient-held expectation that they would be "back to normal again" at the point of discharge from hospital was unrealistic. However, their own expectations regarding the pace of recovery from CAP varied widely, which usually related to their level of experience, amount of

exposure to patients recovering from CAP post-discharge, and their professional specialism. Junior HCPs described how they told patients that *'these things do take 5-7 days for you to get better"* (HCP 9, Junior Doctor), partly to offer some reassurance to patients that they will indeed recover. In contrast, senior HCPs, including senior nursing staff, specialists in Respiratory Medicine and Consultants across all specialities, expected the symptoms and functional impairments associated with CAP to persevere after completion of antibiotics, and that recovery for some could be prolonged; estimates of six months to a year were offered.

Over the course of their illness, patients reported a sense of vulnerability related to different stages of recovery; following their diagnosis with CAP, at the uncertainty of the longer-than-expected recovery process and at the potential long-term health implications of CAP, including susceptibility to recurrent CAP. These reported vulnerabilities were present during initial recovery in some patients but developed in later interviews in others; once their acute illness had begun to resolve and the gravity of their illness had become apparent. This anxiety extended to feeling "*frightened of going*" (Patient 5, interview 2) back to work, or to public areas due to the possibility of exposure to infections leading to a recurrence of CAP; *"your immune system is knackered isn't it, so the likelihood is that if you go in a supermarket where everyone sneezes all over you, you could potentially be picking something else up couldn't you. You're far more vulnerable".* (Patient 10, interview 1).

3.3.2.2; Theme 2: Re-consultation

Concerns over the slow recovery in their condition led some patients to re-consult. These patients attributed their slow recovery to prescription of the wrong antibiotic or dose, or wrong duration, and thus felt it was necessary to re-consult; *"to me it was just a chest infection, but I was on the wrong antibiotics. And I know you can be on the wrong antibiotics, and it doesn't help an infection... I had to go back to the doctors last week because I didn't trust that I was actually getting better or …" (Patient 6, interview 1)*. For others, it was worry regarding further acute deterioration in health, including mortality, which prompted re-consultation to seek medical review for advice about health promotion and lifestyle modification.

Healthcare professionals describe re-consultation to hospital following an episode of CAP as being multifactorial; decompensation of co-morbid illnesses, insufficient social support, baseline frailty, persistent symptoms, and functional impairment. Unrealistic patient expectations regarding the pace of recovery contrasted by the actual slower recovery experienced was a recurring theme cited by HCPs as a reason for re-consultation. *'…I think that's why we get so many readmissions because a lot of patients are discharged, not getting enough information, going home, panicking, phoning 999. A lot of patients still, they'll be coughing up mucus and they seem to think because they're being discharged, that mucus will just go…they just expect everything to clear up straightaway.'* (HCP 13, Staff Nurse), *and 'I think it's the symptoms not improving as they would expect, I guess that maybe due to not receiving enough information when they were in the hospital the first time round, or maybe just having greater*

expectations of themselves that they should be feeling better or more better at that point in time, but that seems to be the main complaint for people coming back, is that their symptoms aren't improving as they would expect.' (HCP 14, Staff Nurse).

3.3.2.3; Theme 3: Support during CAP recovery

Across the three time points in the interviews, patients identified a range of support needs, which were revised and prioritised during their recovery period. Many patients expressed feelings of isolation and an inability to self-manage their on-going symptoms.

Healthcare professionals also expressed that the training and information required to adequately educate patients, facilitate self-care, and focus on patient-centred approaches were lacking. Although HCPs were aware of information leaflets relating to recovery for other acute illnesses such as chronic obstructive pulmonary disease, sepsis, and pulmonary fibrosis, they were not aware of similar information resources for patients recovering from CAP. Patients expressed that when information was provided, it was always verbal and was often vague and non-specific, focusing in the main on the resolution of cough or shortness of breath, which inadequately addressed their needs. They suggested an information resource which included a timeline of recovery from CAP would help manage expectations, '*…I'd would have liked more information on what to expect. I know everybody's different, but I think they could have sort of gave me a general outlook on what to expect.'* (Patient 10, interview 1).

Patients suggested that engagement with HCPs at the point of discharge or shortly thereafter would be the optimum time to provide this information. However, there was limited agreement on how information should be provided, with a combination of resources being suggested by participants including

written information, a telephone helpline, websites and applications, or a specialist nurse service.

Healthcare professionals expressed varied opinions about outpatient follow-up following hospitalisation for CAP. Junior HCPs often lacked clarity regarding the appropriate timing, reason, and place (hospital versus primary care) for review. They expressed conflicting knowledge of post-discharge pathways, delegation of responsibility, follow-up criteria, post-discharge investigations, or routes for readmission. Specifically, there was uncertainty regarding the practice of obtaining a follow-up chest x-ray; when to request one, who should request it and whose responsibility is it to review; "*I've seen some of the x-rays are just reviewed by the GP in some cases, and then there's others that just don't have a follow-up.'* (HCP 1, Junior Doctor) and *'I don't know, to be honest with you. We kind of see them, diagnose them, treat them, and send them home! There's no clear pathway that I know of, as I was saying before about the whole follow-up chest x-ray and things like that, I don't know how often that happens, how often that gets chased, I think we, in hospital medicine at least, we do everything we can here and then everything else gets fobbed off onto the GP, which you could argue for and against…'* (HCP 7, Junior Doctor)

3.4; Discussion

The main findings from this study were; 1) that patients were unprepared for the substantial morbidity associated with CAP, 2) patients experienced a high degree of anxiety during this period, and 3) patients frequently re-consulted healthcare providers due to unmet psychosocial needs.

The slow pace of recovery was consistently described as a debilitating factor, impacting substantially on patient's quality of life. Perspectives on recovery in HCPs were dependent on seniority and experience, with a lack of appreciation for the intrusive impairments experienced by patients contributing to their confusion.

The rapid onset of symptoms above and beyond pre-illness expectations led to anxiety in patients and exposed multiple vulnerabilities. Patients identified a range of information needs which they believed would assist them to self-manage their recovery, lessen their anxiety, improve their understanding, and ultimately facilitate effective self-management

3.4.1; Research in context

In a qualitative study of adults hospitalised with low severity CAP; Baldie *et al.* found that once patients had returned home, they had little understanding of the origins, meaning and the short and long term implications of pneumonia recovery.[93] Most participants in that study also reported that the main symptom they had to manage was extreme tiredness. Based on patient reported symptoms measured using the CAP-symptom score, Wootton *et al.* calculated that symptoms from CAP were resolved by Day 10 from admission in 98% of

adults hospitalised with CAP.[64] In contrast, studies that have measured the time to 'return to normal activity' have found recovery in this domain to take between 15 to 24 days.[13,94] Similarly, others have found that patients recovering from CAP remain 'off work' for between 26 to 30 days.[95] Our study supports the observation that current tools for the quantitative measurement of symptom recovery may not adequately reveal the impacts of CAP on neither functional recovery nor important patient-reported symptoms identified by qualitative methods.

In a multi-centre study, Daniel *et al.* observed that a third of adults who re-consulted their GPs following discharge from hospital with CAP received further antibiotics.[87] Whether such additional antibiotic prescriptions are warranted or microbiologically appropriate is unknown. In the General Practice Patient Survey,[96] antibiotic prescribing was identified as a significant positive predictor of all 'doctor satisfaction' and 'practice satisfaction' scores, reflecting the common belief amongst many patients that 'correct' antibiotics are 'necessary' in acute respiratory infections for complete symptom improvement. We found that patient anxieties in relation to different aspects of CAP recovery, including long-term concerns regarding CAP recurrence, contributed towards re-consultation.

Patients identified important information needs, particularly in relation to the time needed for recovery. The National Institute for Health and Care Excellence (NICE) Pneumonia Guideline recommends that patients should be informed about the expected course of CAP symptom resolution, and advised regarding a

range of timeframes for recovery derived from published studies.[84] However, patients described such information as being too impersonal and rigid. They expressed preferences for more personalised information that describes what to expect in terms of the likely impact on their daily living compared to a timeline of symptom resolution. Patient education in the form of a patient handout compared to standard care was assessed in a North American study for its impact on three primary endpoints; patient knowledge and experience, length of time on intravenous antibiotics and length of hospital stay.[97] The study found that for patients who received education on pneumonia, their knowledge regarding CAP recovery and symptom recognition improved, but there was no improvement in their "worries about problems after discharge". Baldie *et al.* reported that patients recognised that some of the information they required after discharge probably had been provided during their hospital stay, but they had been too ill to listen at the time or had simply forgotten.[93] In a randomised controlled trial conducted in Spain, adults who received an individualised educational programme delivered as two 30-minute sessions pre-discharge were less likely to re-consult healthcare within 30 days of discharge compared those who received conventional information (23.5% vs 42.9% respectively).[95]

3.4.2; Strengths and limitations

To our knowledge, this is the first qualitative study with longitudinal data relating to patient recovery from CAP. The use of qualitative method facilitated a rich and detailed collection of longitudinal data comprising a total of 44 interviews from 15 patients. The perspectives of a wide range of HCPs were also

obtained. Having three researchers conducting the interviews and analysing data broadened the perspective of the work and allowed multiple viewpoints.

One study limitation was the single-site design. In addition, although the study involved patients of various ages recovering from mild to moderate severity CAP, patients with high severity CAP were not well represented; although patients with high severity CAP were approached for study participation, they frequently declined recruitment due multiple factors, including but not limited to illness severity, acute cognitive impairment, and concerns regarding committing to follow-up visits. Whilst it is likely that the main themes identified in this study would apply, at least equally, to patients hospitalised with high severity CAP, other themes specific to recovery from high severity CAP, including treatment in an intensive care unit, may have been missed. Other study limitations include the lack of inclusion of the viewpoints of family or carers, patients whose first language was not English, and GPs.

3.4.3; Implications

This study highlights important unmet patient needs during recovery from CAP that contribute to reduced patient satisfaction and increased post-discharge healthcare re-consultation. Patients discharged with CAP are often left to manage their recovery on their own. Current practice in the timing and method of patient education fails to address patients' needs. Information shared during a hospital inpatient episode should be reinforced and supplemented at the point of discharge or soon after. Much more research is needed to identify

interventions that may improve patient recovery from CAP, including the development of better tools for measuring recovery. Randomised trials to determine the cost-effectiveness of such interventions with respect to clinical and patient-reported outcomes should follow.

3.4.4; Conclusion

Following a hospital admission for CAP, patients are unprepared for the morbidity associated with CAP, experiencing a high degree of anxiety during the slow recovery period. Information provided by healthcare professionals lacks consistency in content or delivery and does not adequately prepare patients for their recovery after discharge. Follow-up care after hospitalisation with CAP should take these views into account.

Chapter 4: Patient Reported Outcome Measures in the recovery of adults hospitalised with community-acquired pneumonia: a systematic review

4.1; Introduction

As discussed in in the introduction, community-acquired pneumonia is a common infectious disease frequently requiring admission to hospital,[6] most patients survive their hospital admission and are discharged to recover, [10,11] there is disparity between physician-assessed, radiographic, and patient-reported recovery, [58,100] and patient-reported outcome measures are advocated by both patients and national governing bodies as providing robust indications of patient-experienced morbidity. [101,102]

Subsequently, recommendations for the development, selection, application, and interpretation of patient reported outcome measures (PROMs) have been proposed to optimise their reliability and validity, [103-107] and a review of outcome measures across all aspects of CAP advocated greater use of PROMs.[108] However, there is no agreed consensus regarding patient-reported outcome measures in CAP recovery. We therefore conducted a systematic review to gather and summarise the available literature regarding PROMs following a hospital admission episode for CAP to inform future research in this area.

4.2; Methods

4.2.1; Study design

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[109] The review protocol was prospectively registered in the PROSPERO database (CRD42017059799).[110]

4.2.2; Study selection

Randomised controlled trials (RCTs), quasi-experimental, and non-randomised studies in adults attending secondary care facilities with a presenting diagnosis of CAP and assessing at least one of the pre-defined patient-reported markers of recovery were included. A diagnosis of CAP was defined as: symptoms and signs consistent with an acute lower respiratory tract infection associated with radiological confirmation of pneumonia on chest x-ray. Attendance at a secondary care facility was defined as any patient receiving their initial review and all or part of their treatment for CAP at an acute hospital facility, including Emergency department visits, with or without subsequent admission.

Two study authors conducted sequential review of identified studies independently, proceeding from title to abstract to full texts, with exclusions at each stage if studies did not fulfil eligibility criteria. Disagreement was resolved by discussion and consensus, involving a third review author as necessary.

4.2.3; Outcome measures

Primary outcomes of interest measured within 6 weeks following hospital discharge were a) patient reported symptoms, b) return to work and/or usual

activities of daily living, and c) healthcare utilisation. Secondary outcomes of interest measured within 6 weeks following discharge were a) proportion with physician determined clinical cure in studies reporting symptomatic and functional recovery, and b) change in quality-of-life scores. (Outcomes occurring within six weeks of discharge were chosen as the time-point for assessment because we anticipated most studies would report outcomes at that time-point, and it coincides with the time-point at which other outcomes are commonly measured in studies of CAP.)

4.2.4; Search Strategy

Comprehensive searches of biomedical electronic databases were conducted: Cochrane Central Register of Controlled Trials (CENTRAL 2017, Issue 3), MEDLINE (1946 to March week 3, 2017), EMBASE (1980 to March 2017), CINAHL (1981 to March 2017), AMED (1985 to March 2017), and Web of Science (1985 to March 2017). The search strategy included subject headings and key words related to community-acquired pneumonia, symptom recovery, functional activity, healthcare utilisation and treatment outcome. The searches were not subject to any language restrictions. Details of the search strategy for each database are found in Table 4.1. An additional grey literature search was conducted using Google Scholar to identify unpublished data of potential significance to the review. Reference lists of included studies were reviewed to identify potentially relevant articles. The full texts of identified articles were reviewed and assessed against eligibility criteria. Conference proceedings of the last 3 years for the American Thoracic Society Conference, British Thoracic Society Winter Meeting and European Respiratory Society Congress were reviewed to identify potentially

eligible articles. Details of all resources used are summarised in Table 4.2. All identified studies were initially exported into Covidence and subsequently Endnote reference management software.

Table 4-1: Search strategy for bibliographic databases

MEDLINE (OVID)	EMBASE (OVID)	AMED (OVID)
1. exp Pneumonia/	1. exp pneumonia/	1. exp Pneumonia/
2. exp Community-Acquired Infections/	2. exp community acquired infection/	2. community-acquired infection*.mp.
3. "community-acquired pneumonia.tw.	3. community acquired pneumonia*.tw.	3. community-acquired pneumonia*.mp.
4. exp "Outcome Assessment (Health Care)"/	4. community-acquired pneumonia*.tw.	4. community acquired pneumonia*.mp.
5. exp "Recovery of Function"/	5. 1 and 2	5. OR/ 1-4
6. exp "Activities of Daily Living"/	6. OR/ 3-5	6. exp "recovery of function"/
7. exp Symptom Assessment	7. exp outcome assessment/	7. exp "Activities of daily living"/
8. exp Treatment Outcome/	8. recovery of function*.mp. or exp convalescence/	8. exp Symptoms/
9. exp Patient Readmission/	9. exp daily life activity/	9. exp Treatment outcome/
10. symptom recovery.tw.	10. exp symptom assessment/	10. exp Rehabilitation/
11. symptomatic recovery.tw.	11. exp treatment outcome/	11. patient readmission*.mp.
12. functional recovery.tw.	12. exp hospital readmission/	12. functional recovery*.mp.
13. 1 and 2	13. symptom recovery*.tw.	13. OR/ 6-12
14. 3 or 13	14. symptomatic recovery*.tw.	14. 5 and 13
15. OR/ 4-12	15. OR/ 7-14	
16. 14 and 15	16. 6 and 15	

Table 4-2: Resources used for literature search

Electronic databases	Other resources
Cochrane Central Register of Controlled Trials (CENTRAL) 2017, www.thecochranelibrary.com - accessed 21st March 2017)	Abstracts from the last 3 years (2015, 2016, & 2017) for
MEDLINE (1946 to March week 3, 2017)	British Thoracic Society Winter Meeting (BTS)
EMBASE (1980 to March 2017)	European Respiratory Society Congress (ERS)
CINAHL (1981 to March 2017)	American Thoracic Society Conference (ATS)
AMED (1985 to March 2017)	Bibliographies of included studies
Web of Science (1985 to March 2017)	

4.2.5; Data extraction

All data were independently extracted by two authors (HP, TM) using a pre-designed form (appendix 1) that was initially piloted on five studies; any disparities were resolved by discussion and consensus, including a third reviewer as required. Where data were represented graphically within studies, DigitizeIt© software (Version 2.3.3, www.digitizeit.de) was used to derive estimated values. Information on study population, outcome, and study design were collected.

4.2.6; Assessment of risk of bias

A specific quality assessment checklist was created for this review, combining relevant aspects from two validated tools.[111,112] The Newcastle-Ottawa scale is a validated tool developed to incorporate quality assessment into the interpretation of meta-analysis results for case-control and cohort studies. It judges studies across three broad categories; study group selection, comparability, and ascertainment of exposure or outcome. The Down's and Black Quality Assessment Tool is a validated checklist to assess the methodological quality of randomised and non-randomised studies and highlight specific areas of methodological weakness to reviewers. These two tools were reviewed and relevant aspects of each selected and combined to form a review specific checklist. Domains from the two validated tools that were determined to be irrelevant to this review were not included. Examples of domains assessed as irrelevant and therefore not included details of study intervention and associated participant compliance. The specifically developed checklist was used to assess details pertaining to study period and location, participant selection, and outcome measure for each included study, with a final total score out of six

(with 0 representing low quality and 6 representing the highest possible quality rating.)

4.2.7; Data synthesis

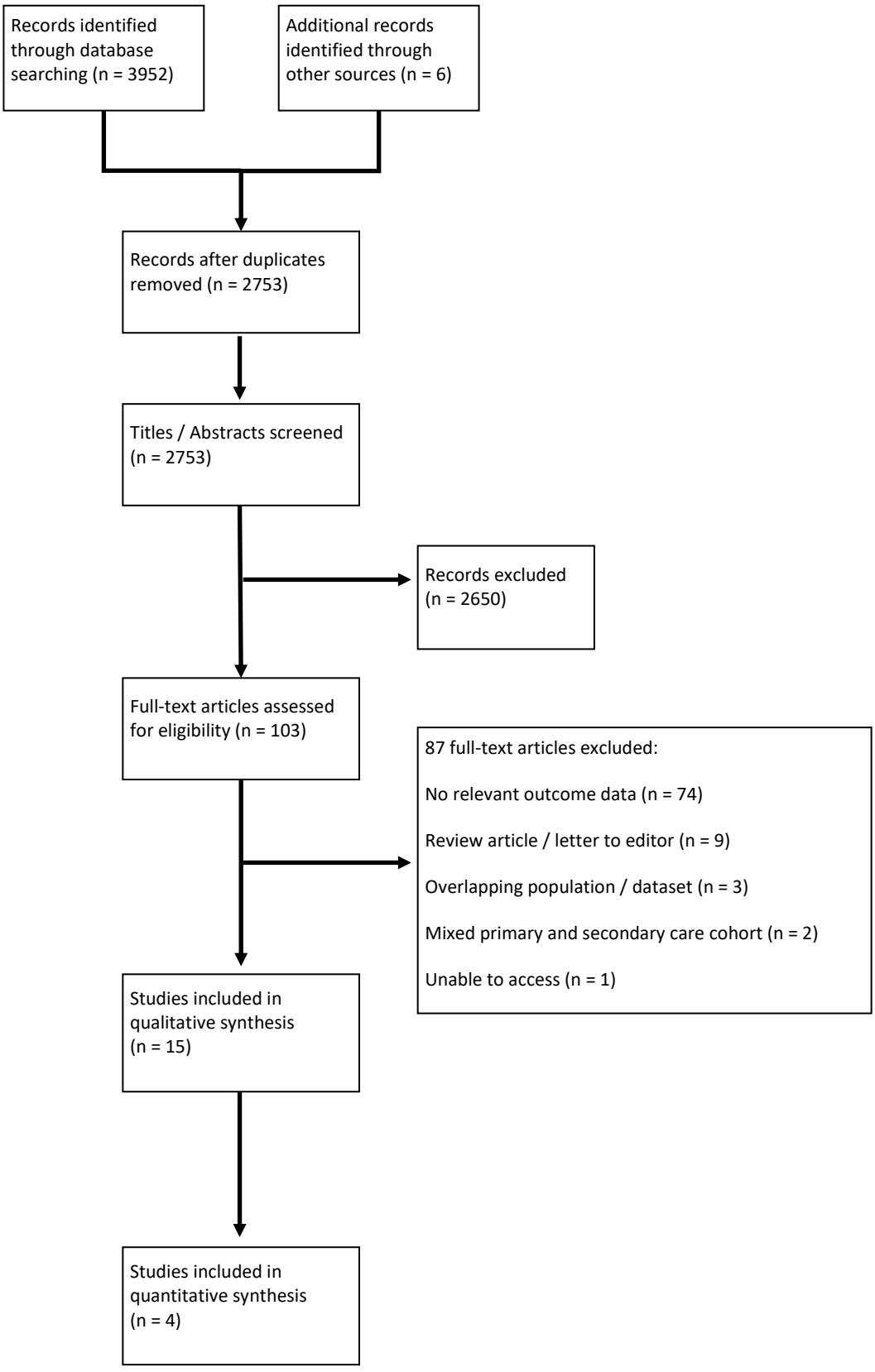
Extracted results were reviewed to assess if adequate similarity existed with respect to outcomes to conduct quantitative synthesis. Meta-analysis was performed using a random effects model where appropriate. The meta-analysis utilised the logit transformation due to its relative simplicity (when compared with arcsine-based transformations) and intuitive interpretation from a practical perspective.

The I^2 statistic was used to assist with assessment of heterogeneity between studies. An I^2 statistic value of greater than 75% was considered to represent substantial heterogeneity between studies. All statistical analysis was conducted using Stata © version 15 (StataCorp. 2017.)

4.3; Results

The search strategy identified 3958 articles, of which 2753 remained after de-duplication and were included in the first stage of study selection (figure 4.1 – study flow diagram). The full texts of 103 articles proceeded to the next stage of study selection, yielding 15 articles for inclusion in the systematic review. The main reasons for article exclusion following full-text review were; lack of relevant outcome data in 73 articles, ineligible article type in 9 articles (review or correspondence), and overlapping or duplicated study population in 3 articles.[13,48,52,54,56,58,63,64,87,94,95,113-116] Of the 15 included articles, four were included in the meta-analysis of symptom prevalence at 4 weeks post-discharge.[13,52,64,87] The remaining 11 articles were included in the narrative synthesis only due to disparity in outcome measures and/or instruments used for their assessment.[48,54,56,58,63,94,95,113-116]

Figure 4-1: PRISMA flow diagram for article selection process



4.3.1; Characteristics of included studies

The characteristics of the 15 included studies are summarised in Table 4.3. Eligible studies included two RCTs, eight prospective cohort studies, one retrospective cohort studies and four studies with cohort data for participants originally enrolled in RCTs. Six studies were restricted to patients with low and moderate severity CAP (Pneumonia Severity Index (PSI) classes I to III, PSI score <110, or CURB65 score 0-2)[52,56,58,87,113,114] or age < 65 years.[52,87] One study did not assess disease severity,[54] and the remaining studies included patients of all disease severities with mean PSI across studies ranging from 76.2 (±32.8) to 106.2 (±23.9).[13,48,63,64,94,95,115,116] Outcome measures of interest varied substantially between the included studies, with variable choice of outcome, tool for assessment, and timing of measurement. Individual study methodology is summarised in Table 4.4.

Table 4-3: Summary of included studies

Author	Country	Study Period	Study Type	Study Population	Outcome
Studies with participants selected for low-moderate severity CAP or Age <65 years (n=6 studies, n=1217 individual participants)					
Bruns 2010[58]	Netherlands	November 2000 - July 2003	Multicentre prospective cohort	119 adults with CAP CAP Aetiology: Streptococcus pneumoniae 27.7% Selection criteria; Age – unselected (mean age 56.6 (±17.8) Severity – low severity, PSI<110 (mean PSI 65.5 (±22.1)) Co-morbid disease – unselected Immune status – unselected	Normalisation CAP score at day 10 – 32.0%, Physician rated clinical cure at day 28 - 88.9%
Carratala 2005[113]	Spain	October 2000 - October 2002	Cohort from Multicentre RCT	224 adults with CAP – 101 patients in hospitalised cohort CAP Aetiology: Streptococcus pneumoniae - 14.0%, Legionella pneumophila - 4.4, Haemophilus influenzae - 2.6%, "Atypical" - 2.6% Selection criteria; Age – unselected (mean age; outpatient group 67.5 (±11.8), inpatient group 64.9 (±13.4)) Severity – low severity, PSI classes II & III (Mean PSI outpatient group 70 (±11.6), inpatient group 66.9 (±12.5)) Co-morbid disease – excluded if pregnant, breast feeding, respiratory failure, concomitant unstable comorbid conditions necessitating hospitalisation, complicated pleural effusion, lung abscess, shock, metastatic infection, severe social problems, cognitive impairment, psychiatric disease. Immune status – immunocompetent only (excluded HIV, splenectomy, immunosuppressive therapy, corticosteroid therapy, neutropenia, solid organ transplant) Other – excluded if quinolone allergy or quinolone therapy in preceding 3 months	SF-36 score; "At 30-day follow-up SF-36 scores remained abnormal, but had returned towards baseline for Spanish population"

Author	Country	Study Period	Study Type	Study Population	Outcome
Daniel 2018[87]	UK	February 2015 - April 2016	Multicentre prospective cohort	108 adults with CAP, Male – 48.2% CAP Aetiology: Streptococcus pneumoniae – 16.7% Selection criteria; Age – 18-65 years only (median age 50 (IQR 38.3-57.8)) Severity – unselected (CURB65 0-1 = 88.9%, CURB65 2 = 9.3%, CURB65 $\geq$ 3 = 1.8%) Co-morbid disease – unselected Immune status – unselected	Proportion of patient reporting prevalence of symptoms and functional impairment at 28days following discharge; Cough – 31.9%, Dyspnoea – 27.5%, Chest pain – 16.5%, Sputum – 11.0%, Fatigue – 12.1%, 1 or more symptom – 58.2% Not returned to ADLs – 51.1% No to returned to Work 34.3% Re-consultation within 28 days; ED attendance – 12.0% Primary care – 59.2%
El Moussaoui 2006[114]	Netherlands	November 2000 - July 2003	Cohort from Multicentre RCT	91 adults with CAP, Male 58.8% CAP Aetiology: Streptococcus pneumoniae – 23.8% Selection criteria; Age – unselected (median age 65 (IQR 48-72)) Severity – low severity, PSI <110 (mean PSI 71 (±23) Co-morbid disease – excluded if pregnant, severe underlying disease, preceding antibiotic treatment for >24 hours prior to admission, concurrent co-morbid disease likely to interfere with course of pneumonia, respiratory failure Immune status – unselected Other – excluded if amoxicillin allergy	Median CAP scores (IQR) Day 3 – 56 (38-69) Day 7 – 60 (37-75) Day 10 – 65 (37-86) Day 14 – 77 (61-88) Day 28 - 75 (58-93)

Author	Country	Study Period	Study Type	Study Population	Outcome
Laberere 2007[56]	USA / Canada	January 2001 - December 2001	Cohort from Multicentre RCT	549 adults with CAP, Male 44% CAP Aetiology: Not reported Selection criteria; Age – unselected (median age 66 (IQR 48-77) Severity – low severity, PSI classes I-III (PSI I – 16.0%, PSI II – 41.0%, PSI III – 43.0% Co-morbid disease – excluded if pulmonary tuberculosis, alcoholism & evidence of end-organ damage, social problems incompatible with recruitment, illicit drug use 30days Immune status – immunocompetent only (excluded if HIV, immunosuppression)	Median time for return to ADLs Workers - 22 days (11-29) Non-workers - 20 days (9-29) Median time return to work - 14 days (8-29)
Metlay 1998[52]	USA	April 1996 - February 1997	Single centre prospective cohort	126 adults with CAP Male – 54.8% CAP Aetiology: Not reported Selection criteria; Age – 18 to 64 years Severity – low severity, PSI classes I-III (mean PSI 55.2) Co-morbid disease – excluded if pregnancy, severe neuromuscular disease Immune status – immunocompetent only (excluded if chronic immunosuppression or HIV.) Other – nursing home residence, psychological or social problems compromising follow-up	Proportion of patient reporting prevalence of symptoms at 28days following discharge; Cough – 19.9%, Dyspnoea – 16.8%, Fatigue – 25.7%, Fever – 3.5%, 1 or more symptom – 35.0%

Author	Country	Study Period	Study Type	Study Population	Outcome
Studies where participants were unselected for severity or age (n=9 studies, n=4427 individual participants);					
Adamuz 2011[48]	Spain	January 2007 - December 2009	Single centre prospective cohort	828 adults with CAP, Male – 65.8% CAP Aetiology: Streptococcus pneumoniae – 44.1%, Legionella pneumophila – 3.0%, Haemophilus influenzae – 4.4%, Anaerobes – 5.6% Selection criteria; Age – unselected (median age 71 (IQR 55-79)) Severity – unselected (PSI>90 IN 62.2%) Co-morbid disease – unselected Immune status – immunocompetent only (excluded HIV, splenectomy, immunosuppressive therapy, corticosteroid therapy equivalent to prednisolone >20mg daily, neutropenia, Ig deficiency, solid organ transplant) Other – excluded if inpatient death	Healthcare utilisation at 30 days ED – 21.4%, Primary Care – 18.0% Symptoms reported in participants re-consulting within 30days; Primary care (n=149) Respiratory symptoms – 75.2% General symptoms – 22.8% ED (n=177) Worsening pneumonia symptoms – 47.5%
Adamuz 2015[95]	Spain	January 2011 - October 2014	Multicentre RCT	207 adults with CAP, Male – 59.9% CAP Aetiology: Streptococcus pneumoniae – 24.6%, Haemophilus influenzae – 5.4%, Influenzae A – 3.4% Selection criteria; Age – unselected (21-49 = 20.2%, 50-69 = 30.5%, >70 = 49.3%) Severity – unselected (CURB65 0-1 = 49.3%, CURB65 2 = 34.3%, CURB65 $\geq$ 3 = 16.4%) Co-morbid disease – Excluded cognitive impairment Immune status – immunocompetent only (excluded HIV, splenectomy, immunosuppressive therapy, corticosteroid therapy equivalent to prednisolone >20mg daily, neutropenia, Ig deficiency, solid organ transplant) Other – excluded if nursing home resident or long-term care facility, language barrier	Healthcare utilisation at 30daysPrimary care – 20.3% ED – 18.4% Median time off work; Intervention group – 30 days (IQR 15-66.5) Usual care group – 26 days (IQR 12.5-37)

Author	Country	Study Period	Study Type	Study Population	Outcome
Fine 1999[13]	USA / Canada	October 1991 - March 1994	Multicentre prospective cohort	1343 adults with CAP, Male 52.4% CAP Aetiology: Streptococcus pneumoniae – 9.1%, Haemophilus influenzae - 4.8%, "Atypical" – 2.1%, Enterobacter sp. – 2.8%, Pseudomonas aeruginosa – 0.9% Selection criteria; Age > 65years 58.7% Severity – unselected (PSI I – 13.8%, PSI II – 17.4%, PSI III – 18.9%, PSI IV – 33.2%, PSI V – 16.7%) Co-morbid disease - unselected Immune status – excluded if HIV	Proportion of patient reporting prevalence of symptoms and functional impairment at 30days following discharge; Cough – 47.1%, Dyspnoea – 46.5%, Sputum – 42.3%, Fatigue – 72.6%, 1 or more symptom – 68.5% Not returned to ADLs; Workers – 18% (median 15days) Non-workers – 42.8% (median 24 days) Not returned to work 31.9%
Marrie 2000[115]	Canada	January 1998 - July 1998	Multicentre prospective cohort	535 adults with CAP, Male – 52.3% CAP Aetiology: Not reported Selection criteria; Age – unselected (mean age 61.6 (±19.1) Severity – unselected (mean PSI 76.2 (±32.8) Co-morbid disease - unselected Immune status – unselected	Proportion of patient reporting prevalence of symptoms and functional impairment at 14days and 42days following discharge; Cough – 55.8%, 35.3% Dyspnoea – 48.6%, 34.2% Chest pain – 17.3%, 11.6% Sputum – 35.9%, 26.4% Fatigue – 66.7%, 45.0% Fever – 8.4%, 4.7% 1 or more symptom – 85.6%, 64.3%
Nickler 2016[116]	Switzerland	October 2006 - March 2008	Cohort from Multicentre RCT	753 adults with CAP, Male 58.8% CAP Aetiology: Not reported Selection criteria; Age – unselected (median age 72 (IQR 52-82) Severity – unselected (PSI I – 10.0%, PSI II – 19.7%, Co-morbid disease – excluded if terminal illness Immune status – immunocompetent only (excluded if long-term immunosuppression) Excluded if language impairment precluding consent, IV drug abuse	EQ-5D index – decline in ADLs in 29% at day 30

Author	Country	Study Period	Study Type	Study Population	Outcome
Sharma 2006[63]	USA	March 1995 - March 1998	Single centre prospective cohort	79 adults with CAP, Male – 35% CAP Aetiology: Not reported Severity criteria; Age – unselected (mean age 79.9 (±6.1) Severity – unselected (mean PSI 106.2 (±23.9) Co-morbid disease – excluded if terminal illness Immune status – unselected Other – excluded if coma, intensive care admission, unable to participate in interview	Proportion with decline in ADL score of greater than 1 point - 22/79 (28%) at day 30
Uranga 2016[94]	Spain	January 2012 - August 2013	Multicentre Randomised Control Trial	312 adults with CAP, Male 62.8% CAP Aetiology: Streptococcus pneumoniae – 16.0%, Legionella pneumophila – 3.5%, Haemophilus influenzae – 0.3% Selection criteria; Age – unselected (mean age 62.2 (±6.07) and 64.7 (±18.7)) Severity – unselected (mean PSI 83.7 (±33.7) and 81.8 (±33.8)) Co-morbid disease – unselected Immune status – immunocompetent only (excluded if HIV, immunosuppression for solid organ transplantation, splenectomy, receiving ≥10mg/d of prednisone or the equivalent for >30 days, taking other immunosuppressive agents, or neutropenia) Other – excluded if care home resident, antibiotics within preceding 30 days, intercostal chest drain, extra-pulmonary manifestations, death, or ICU admission prior to randomisation	Mean CAP symptom score at 5 days 24.7(±11.4) to 27.2(±12.5) Mean CAP symptom score at 10 days 18.6(±9.0) to 17.9(±7.6) Median time for return to normal activity 15days (IQR 10-21) to 18days (IQR 9-25)

Author	Country	Study Period	Study Type	Study Population	Outcome
Wootton 2017[64]	UK	February 2011 - March 2013	Multicentre prospective cohort	169 adults with CAP, Male 52% CAP Aetiology: Not reported Selection criteria Age – unselected (mean age 68 (range 16-98) Severity – unselected (CURB65 0-1 = 46.7%, CURB65 2 = 29.6%, CURB65 ≥3 = 23.7%) Co-morbid disease – excluded if bronchiectasis, cystic fibrosis, advanced malignancy Immune status – unselected Other – excluded if palliative treatment, invasive ventilation	Average CAP symptom score - 23.8 at day 2 Average CAP symptom score - 13.6 at day 28 Proportion of patient reporting prevalence of symptoms at 28days following discharge; Cough – 13.6%, Dyspnoea – 67.1%, Chest pain – 31.2%, Fatigue – 57.0%, 1 or more symptom – 96.4%
Wyrwich 2015[54]	USA	Unknown	Multicentre retrospective cohort	201 adults with CAP, Male – 45% CAP Aetiology: Not reported Selection criteria; Age – ≥50 years Severity – unselected Co-morbid disease – unselected Immune status – unselected Other – respondent to email survey, excluded in nursing home resident	Average time to symptom resolution, in days; Cough; mean 13.6, median 7 (2-14) Dyspnoea; mean 25.1, median 14 (7-43) Chest pain; mean 12.9, Median 7 (2-14) Sputum; mean 14.8, Median 7 (7-14) Fatigue; mean 25, Median 20 (7-24) Fever; mean 2.7, Median 2 (1-2) Median time for return to work – 14 days

Table 4-4: Summary of methodologies employed in included studies

Study	Destination after initial review		Severity		Outcome Measure										Timing of assessment of outcome measure (days)				
					Assessment of Symptoms			Health Status		Assessment of function (return to)		Clinical Cure	Healthcare utilisation						
	I/P	O/P	CURB-65	PSI	Prevalence Symptoms	CAP Score	CAP-symptom score	SF-36	EQ-5D	ADLs	Occupation		Primary Care	ED	Average time to X	≤14	28	30	42
Studies with participants selected for low-moderate severity CAP or Age <65 years (n=6 studies, n=1217 individual participants)																			
Bruns 2010[58]	X			X		X						X				X	X		
Carratala 2005[113]	X	X		X				X										X	
Daniel 2018[87]	X		X		X					X	X		X	X			X		
El Moussaoui 2006[114]	X			X		X										X	X		
Laberere 2007[56]	X	X		X						X	X				x				
Metlay 1998[52]		X		X	X												X		
Studies where participants were unselected for severity or age (n=9 studies, n=4427 individual participants);																			
Adamuz 2011[48]	X			X	X								X	X				X	
Adamuz 2015[95]	X		X								X		X	X	X			X	
Fine 1999[13]	X	X		X	X					X	X							X	
Marrie 2000[115]	X	X		X	X											X			X
Nickler 2016[116]	X			X					X									X	
Sharma 2006[63]	X			X						X								X	
Uranga 2016[94]	X			X			X			X					X	X			
Wootton 2017[64]	X		X		X		X								X		X		
Wyrwich 2015[54]	X	X			X						X				X				

4.3.2; Risk of bias in included studies

The risk of bias in included studies is summarised in Table 4.5. Across all included studies the median quality score was 4.5 (IQR 4-5.) Three studies scored full marks at quality assessment.[94,95,113] All included studies defined their follow-up period, with all but a single study adequately defining study population and study period. The study populations were often restricted by selection criteria, such as age, severity of disease, level of dependency or residential status, see Table 4.3, but these selection criteria were deemed appropriate when study design and outcomes of interest were considered. Included studies rarely reported loss to follow-up.

Table 4-5: Risk of bias in included studies

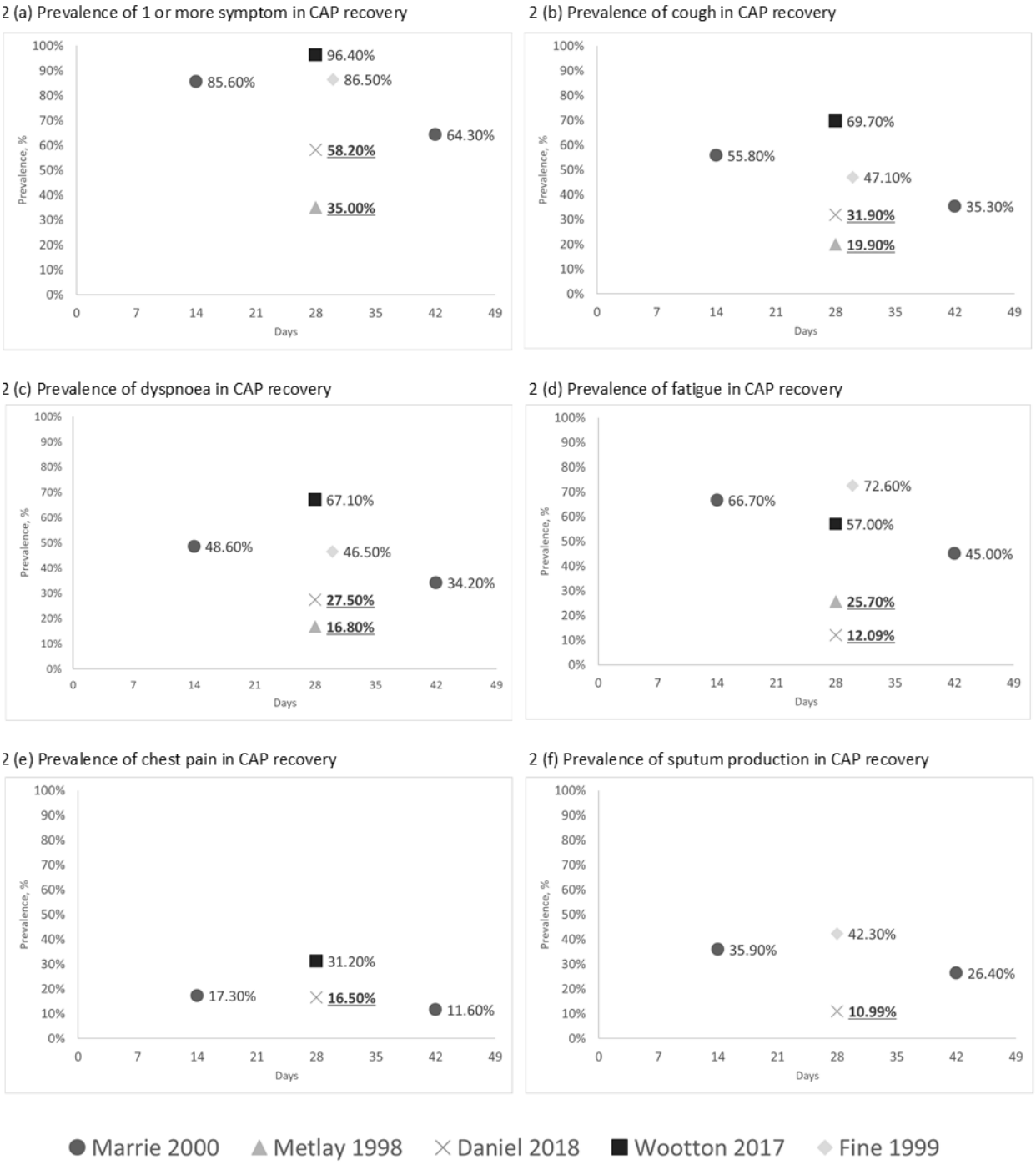
First Author	Selection Domain (max 3)	Outcome Domain (max 3)	Comments
Adamuz 2011	3	2	Outcome measure not clearly defined or justified
Adamuz 2015	3	3	
Bruns 2010	2	2	20.1% loss to follow-up
Carratala 2005	3	3	Low severity CAP (PSI classes II and III only)
Daniel 2018	2	3	Working age adults, low severity CAP
El Moussaoui 2006	2	2	Low severity CAP
Fine 1999	2	2	
Labarere 2007	2	3	Low severity CAP
Marrie 2000	2	2	No details regarding loss to follow-up
Metlay 1998	2	2	
Nickler 2016	2	2	Not representative sample excluded elderly, dementia, significant co-morbid disease
Sharma 2006	2	2	Not representative sample, from cohort study of delirium in elderly, no details on loss to follow-up
Uranaga 2016	3	3	
Wootton 2017	2	2	Excluded patients with cognitive impairment, no loss to follow-up information
Wyrwich 2015	0	2	

4.3.3; Patient reported symptoms

Six studies included data for patient-reported prevalence of symptoms within 6 weeks of discharge.[13,48,52,64,87,115] Four studies reported prevalence of symptoms for participants unselected for age or disease severity.[13,48,64,115] At 28–42 days post-discharge, the commonest symptom reported was fatigue (range: 45% to 72.6% of patients), followed by cough (range: 35.3% to 69.7%) and dyspnoea (range: 34.2% to 67.1%) (Figure 4.2).[115] [13,64] One study of patients attending for healthcare review within 30-days of discharge observed that respiratory symptoms were reported in 75.2% of those attending primary care and 47.5% of those attending emergency departments.[48] Restricting the population to working adults, two studies reported symptom prevalence at 4 weeks following discharge and found 1 or more symptom was reported by 35.0% and 58.2% of participants, cough by 19.9% and 31.9%, dyspnoea by 16.8% and 27.5%, and fatigue by 12.1% and 25.7%.[52,87] Chest pain (16.5%) and sputum production (11%) were reported by participants respectively in one of these studies.[87]

Finally, in an email survey investigating average time for resolution of symptoms following CAP in adults aged ≥50 years (n=500), median time for resolution of cough was 7 days (IQR 2-14), dyspnoea 14 days (IQR 7-43), chest pain 7 days (IQR 2-14), sputum production 7 days (IQR 7-14), fever 2 days (IQR 1-2), and fatigue 20 days (IQR 7-24).[54]

Figure 4-2: Prevalence of symptoms in recovery following community-acquired pneumonia



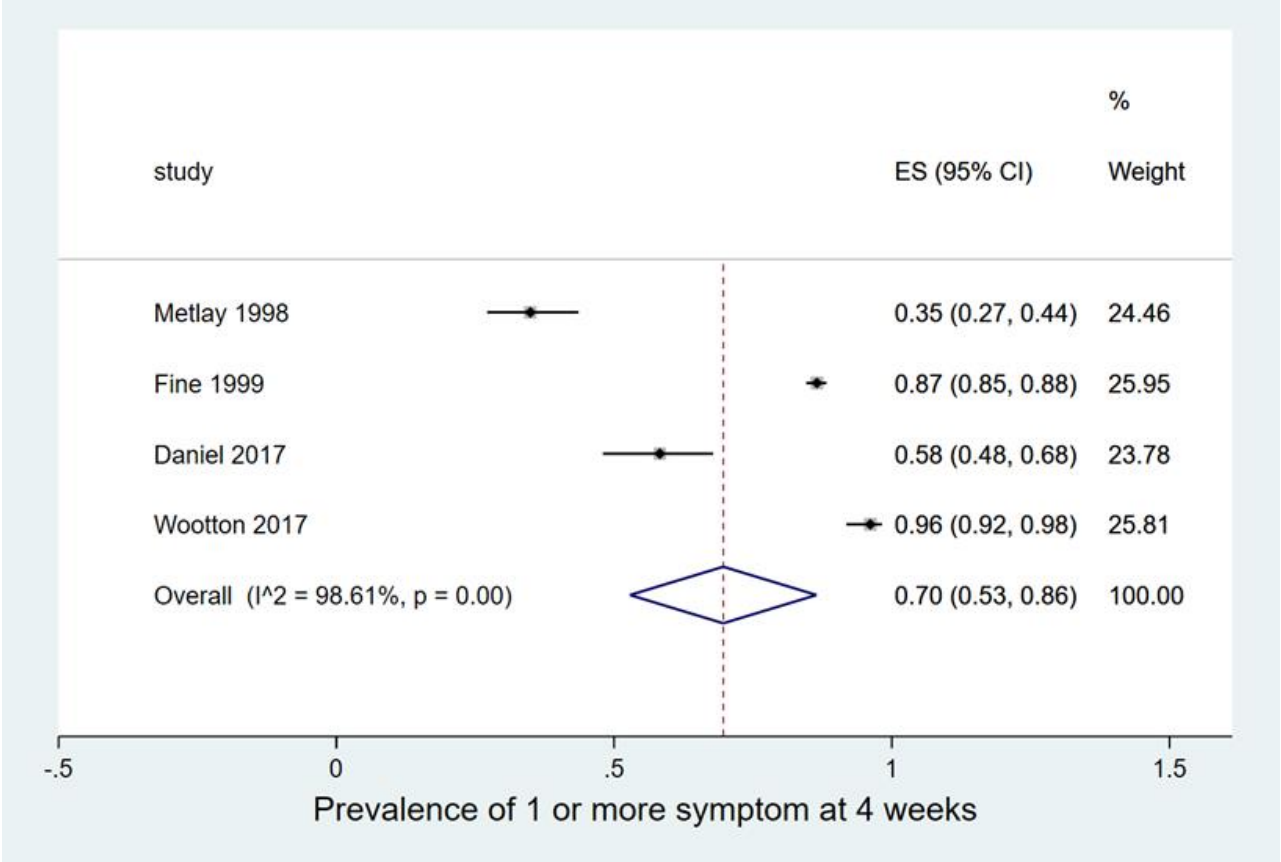
* Studies in bold and underlined are from studies of patient cohorts restricted to either low-moderate severity CAP (PSI Class III or less, CURB65 0-2) or age < 65 years, by design. Marrie et al measured symptom prevalence twice (14days and 42 days), all other studies measured symptom prevalence once.

4.3.4; Quantitative synthesis

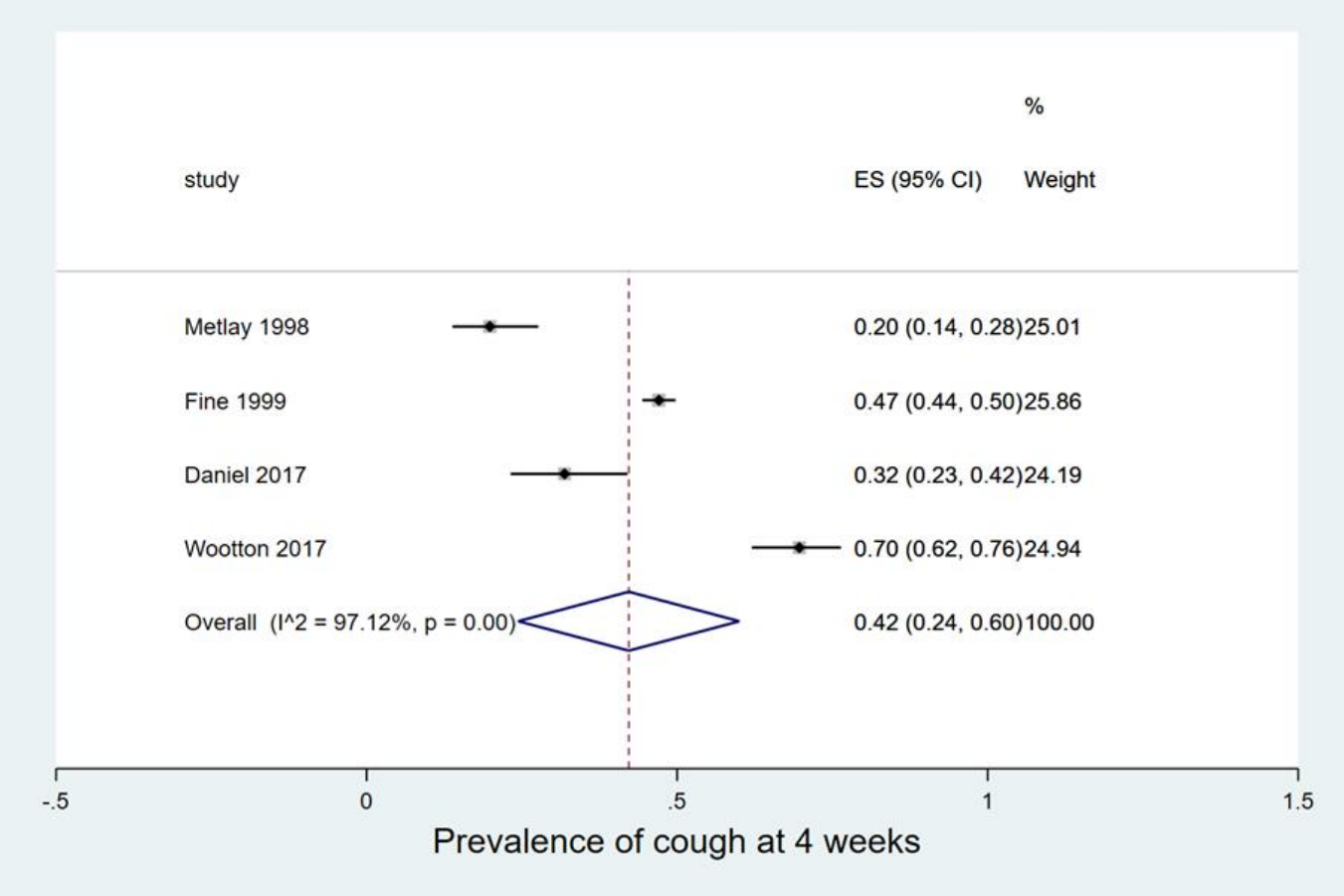
Random effects meta-analysis was performed on amenable data from 4 studies (n=1715) reporting prevalence of symptoms at 4 weeks. [13,52,64,87] High levels of heterogeneity were evident, with the I^2 statistic consistently exceeded 95%. Summary estimates of the proportion of patients reporting; 1 or more symptoms was 70% (95% CI 53% to 86%, I^2=98.6%), cough 42% (95% CI 24% to 60%, I^2=97.1%), dyspnoea 39% (95% CI 21% to 58%, I^2=97.5%), and fatigue 42% (95% CI 10 % to 74%, I^2=99.2%) (Figure 4.3 a - d.)

Figure 4-3: (a) to (d); Random effects meta-analysis of prevalence of symptoms at 4 weeks following discharge from hospital with community-acquired pneumonia.

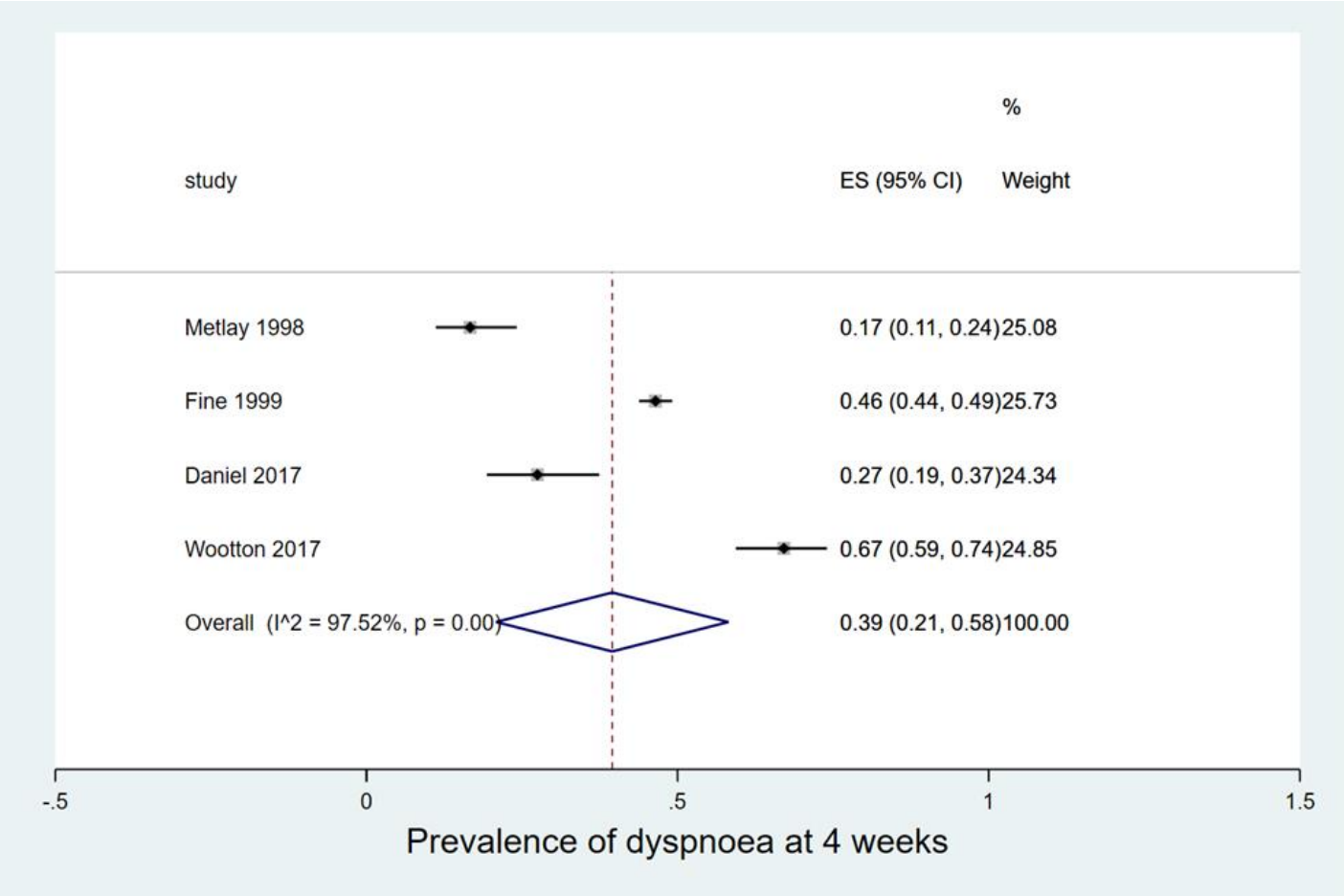
(a) Prevalence of 1 or more symptom at 4 weeks



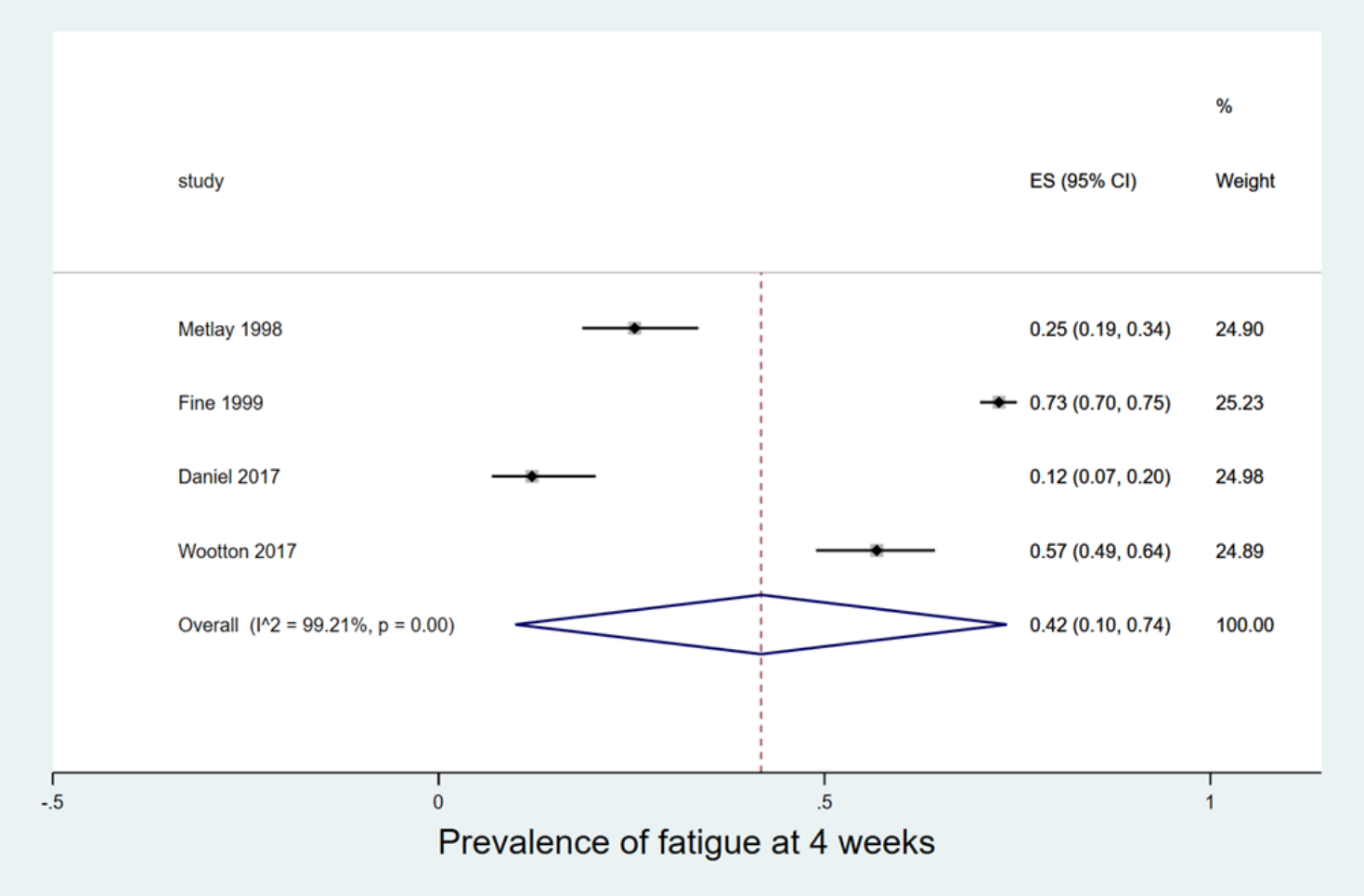
(b) Prevalence of cough at 4 weeks



(c) Prevalence of dyspnoea at 4 weeks



(d) Prevalence of fatigue at 4 weeks



4.3.5; CAP specific symptom scores

Four studies included data derived from pneumonia symptom scores.[58,64,94,114] Two studies (n=91 and n=95) used the CAP score (higher score signifying fewer symptoms); The median CAP scores reported by El Moussaoui *et al* at days 3, 7, 10, 14 and 28 following admission were 56 (IQR 38-69), 60 (IQR 37-75), 65 (IQR 37-86), 77 (IQR 61-88) and 75 (IQR 58-93), and Bruns *et al* reported that normalisation of CAP score, relative to retrospectively assessed baseline scores 6 weeks prior to admission, occurred in 32% of patients at 10 days following hospital admission, and 41.8% of patients at 28 days.[58]

Two studies (n=169 and n=312) used the CAP-symptom score (*lower* score signifying fewer symptoms); Wootton *et al* observed the average CAP-symptom score at day 2 from admission was 23.8 and at day 28 was 13.6, [64] Uranga *et* al, in an interventional trial of short course antibiotics, reported that average CAP-symptom score in the control group on Day 5 from admission was 24.7 (±11.4) and on Day 10 was 18.6 (±9.0) with corresponding values in the intervention group of 27.2 (±12.5) and 17.9 (±7.6).[94]

4.3.6; Return to functional activity

Five studies included data for time to return to normal activities[13,56,87,94,95]. Daniel *et al* found that 51.1% of adults aged below 65 years had not resumed baseline ADLs at 4 weeks.[87] In contrast, Fine *et al* found that 18.0% of 'workers' had not resumed baseline ADLs at 4 weeks compared to 42.8% of 'non-workers'.[13]

The median time for return to normal activity reported by Uranga *et al* was 18 days (IQR 9-25) in the control group and 15 days (IQR 10-21) in the intervention group.[94] Fine *et al* found the median time for return to ADLs in workers was 15 days and in non-workers was 24 days[13] whereas Labarere *et al* found little difference in the median time for return to ADLs between workers (22 days (IQR 11-29)) and non-workers (20 days (IQR 9-29)).[56]

Of two studies with relevant data, 34.3%[87] and 31.9%[13] of participants had not returned to work at 4 weeks. Median time for return to work following discharge was 14 days.[54,56] Adamuz *et al* reported that the median time taken off work by participants in the control group was 26 days (IQR 12.5-37) compared to 30 days (IQR 15-66.5) in the intervention group.[95]

4.3.7; Healthcare utilisation

In addition to PROMs, three studies reported rates of Primary Care consultation and/or Emergency Department (ED) attendance within 4 to 6 weeks following hospital discharge.[48,87,95] Daniel *et* al found that 59.2% had consulted primary care and 12.0% had attended EDs within 4 weeks.[87] This compares with 18.0% and 20.3% attending primary care, and 18.4% and 21.4% attending EDs in the two studies from Adamuz *et al*.[48,95] Of those re-consulting a GP, on-going or new respiratory symptoms were reported by 68.8% to 75.2% of patients. Pneumonia-related symptoms or signs were the reported reason for ED attendance in 47.5% to 84.6% of patients.[87,95]

4.3.8; Other outcomes

In relation to quality of life measures, a single Spanish study commented that "SF-36 score at 30 days following hospital discharge remained abnormal when compared to the reference scores for the Spanish population," but no data were reported.[113] Using the EQ-5D index, Nickler et al noted that 29% of participants exhibited a decline in ADLs at 30 days and that the decline was associated with levels of pro-adrenomedullin and pro-atrial natriuretic peptide.[116]

Physician assessed clinical cure was noted by Bruns et al in 88.9% of participants 28-days after discharge though only 41.7% of patients reported normalisation of symptoms and function (based on the CAP score) at the same time point.[58] No data were provided on any correlation between clinical cure and CAP score.

4.4; Discussion

This systematic review confirms that a high proportion of patients report substantial symptomatic and functional impairments during the first 6 weeks of recovery following hospitalisation with CAP. These are accompanied by adverse impacts on the performance of 'normal activities', such as return to work, and healthcare utilisation. Fatigue, cough, and dyspnoea are the commonest symptoms reported. The prevalence of symptoms over the first 6 weeks of recovery varies across studies in accordance with severity of CAP and age of study cohorts.

Most studies assessed the prevalence of symptoms and functional impairment at specific times (most commonly 4 weeks post-discharge) without reference to baseline prevalence. Given the high proportion of patients with chronic cardiac and respiratory conditions within study cohorts, this approach likely overestimates the contribution of acute pneumonia to the prevalence of patients' symptoms during recovery. That said, studies that measured PROMs at multiple time points during recovery all reported a declining trend in the prevalence of symptoms over time, up to 42 days post-discharge.[58,64,114,115] These findings suggest that many patients continue to have symptoms related to the acute pneumonia episode even at 6 weeks post-discharge, and that these continue to resolve with increasing time from acute infection.

Fatigue is the commonest symptom to be reported during recovery. The importance of fatigue as a contribution towards reduced functional recovery in CAP has not been widely examined. In a qualitative study of patients with low-

severity CAP, both extreme tiredness and need for sleep were reported as prominent symptoms during recovery.[117] Quantitatively, the CAP-symptom score captures the degree of fatigue on a scale of 0-5.[118] However, these assessments do not adequately reflect the complexity of fatigue as a symptom, nor its impact on functional recovery. In other conditions where fatigue is a prominent symptom, validated disease-specific, multi-dimensional tools have been developed to better quantify and assess fatigue.[119,120]

Return to functional activity, measured as return to 'normal activities or ADLs, was consistently reported as taking a median of 15 to 25 days in included studies. This measure is set alongside other included studies that consistently reported a large proportion of patients failing to resume normal activities within 4 weeks post-discharge. One study, not included in this review, found that at 6 weeks post-discharge, 12% of elderly persons had required a change of residence indicating a greater level of dependency.[121] Overall, these studies suggest that the full burden of adverse health outcomes following an episode of CAP is likely to be higher than reflected in measures of symptom resolution alone.[122] Experience from patients recovering from exacerbations of COPD where impaired lung function, exercise capacity, and quality of life persists despite apparent symptomatic resolution provides further support for this view.[123-125]

We identified only two relatively small studies that attempted to describe the correlation between PROMs and healthcare re-consultation.[48,87] These studies suggest that persistence of pneumonia related symptoms is a major factor in GP

re-consultations, while new or worsening comorbid illnesses increase in prominence in relation to ED re-attendances. An episode of pneumonia may be a marker for frailty or increased susceptibility to illness from non-pneumonia related factors.[19] A better understanding of the association between PROMs, long-term complications and healthcare re-consultations is necessary if appropriate interventions are to be developed.

4.4.1; Strengths and limitations

As far as we know, this is the first systematic review of studies assessing PROMs in recovery from CAP. This review was conducted in accordance with PRISMA guidelines. Eligibility criteria were designed to focus the review on studies of patients with CAP and not on cohorts with hospital-acquired pneumonia or aspiration pneumonia.

We found only a small number of high-quality research studies in this field compared to the large burden of disease. Existing studies are disparate in their study populations (age, co-morbid illness, and disease severity) and outcome measures. Importantly, there is a lack of consistency across studies in the choice and application of measurement tools to assess PROMs. The CAP-symptom score is the only available PROM psychometrically validated using a recognised approach, albeit only in an out-patient setting. Indeed, a recent systematic review of the application and content validity of PROMS in CAP concluded that the instruments used to measure recovery are inconsistent in constructs measured and have been developed in study populations which are not representative of the CAP population.[126] These variations in outcome measures

precluded many studies from the planned meta-analysis; the resulting meta-analysis retained high study heterogeneity. Most notably, the meta-analysis illustrates how, at a given time-point, the severity of CAP and / or age of the study cohort greatly affects estimates of symptom prevalence.

4.4.2; Implications

There is an important need for researchers to develop *and* agree on appropriate tools and methodology in the assessment of PROMs during recovery from CAP. Barlow et al previously defined core outcomes sets for CAP research, including recommending the CAP-symptom score for use in studies of recovery. [101] Ideally, the CAP-symptom score should be externally validated for hospitalised patients and a multi-dimensional CAP-specific tool for assessing fatigue developed. Additionally, as recommended by Lloyd et al, any specific instruments developed for assessing CAP recovery in the future need to carefully consider their construct, application, and validity to ensure they are valuable and reproducible measures of patient-reported morbidity.[127]

In the meantime, considering the available evidence, we suggest the CAP-symptom score remains the most appropriate tool for the measurement of CAP-specific symptoms. As the prevalence of symptoms remains high for 2 – 4 weeks post-discharge, and healthcare re-consultation is concentrated to within the same period, we suggest that PROMs should be assessed, at a minimum, twice post-discharge, at around 2 weeks and again at 4 or 6 weeks. To enable analysis of the degree of recovery at these time-points, an assessment at the time of hospital discharge is necessary, together with an assessment of 'pre-pneumonia

baseline. These interim suggestions should be refined as new, stronger evidence emerges and our understanding of recovery from CAP increases.

4.4.3; Conclusion

Morbidity from CAP continues for a sizeable proportion of patients up to at least 6 weeks post-discharge from hospital. There is a large relative lack of high-quality research in this field.

Chapter 5: Readmission rate and associated risk factors for adult patients discharged following an episode of Community-acquired pneumonia; a systematic review and meta-analysis

5.1 Introduction

Studies of CAP frequently report 30-day readmission rate as a primary or secondary outcome measure, [108] and in parts of North America and Europe 30-day readmission rate has been adopted by commissioners as a marker of inpatient quality of care.[101,128,129] In these systems healthcare providers incur pecuniary penalties for readmission rates which diverge from acceptable boundaries, usually defined by degree of deviation from an adjusted median rate.[128-130] Given the potential implications of divergent readmission rates there is now substantial interest in measuring, predicting, and reducing 30-day readmission rate following an episode of pneumonia. A previous systematic review of model performance for predicting risk of 30-day readmission in patients with pneumonia demonstrated that 30-day readmission rates varied substantially (11.8% to 20.8% in included studies), that a limited number of validated pneumonia-specific prediction models existed, and that these models exhibited modest predictive ability.[131] Indeed, readmission rates for numerous different acute medical conditions vary substantially between and within healthcare systems.[132-134] It has been suggested that readmission following an acute medical presentation is dependent on a complex interplay of multiple different factors, including but not limited to patient-related, healthcare-related, socioeconomic, and co-morbidity factors.[135-139] It is likely that these factors vary from patient to patient, between healthcare providers, and across geographical regions.

This review aims to facilitate comparison and understanding of 30-day readmission rate within and between healthcare systems by systematically

summarising; a) the 30-day readmission rate for adult patients hospitalised with an episode of CAP, b) proportion of cases attributed as pneumonia-related or cardiovascular-related, and c) the associated risk factors for readmission.

5.2 Methods

5.2.1 Study Design

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[109] and was prospectively registered in the PROSPERO database (CRD42017082265).[140]

5.2.2 Study selection

Randomised controlled trials (RCTs), quasi-experimental, and non-randomised studies in adults admitted to secondary care facilities with a presenting diagnosis of CAP and reporting 30-day readmission rate as either a primary or secondary outcome were included. To fulfil eligibility criteria, studies were required to define CAP as a constellation of signs and symptoms consistent with acute lower respiratory tract infection (LRTI) and have evidence of acute radiographic features consistent with pneumonia. Studies using coded data (World Health Organisation International Classification of Disease or equivalent) to identify cases of pneumonia were required to apply further eligibility criteria to reasonably determine that included cases were diagnosed with an episode of community-acquired pneumonia and cases of hospital-acquired pneumonia (HAP), post-obstructive pneumonia due to lung cancer, and aspiration pneumonia were excluded. Studies including individuals treated exclusively as outpatients, or in emergency departments and ambulatory care clinics without admission to hospital, were excluded.

Two study authors reviewed identified studies independently (Two of; HP, AK, TM, or DA). Titles, abstracts, and then full texts were reviewed sequentially with

exclusions at each review stage if studies did not fulfil eligibility criteria. Disagreement was resolved by discussion and consensus, involving a third review author as necessary.

5.2.3 Outcome measures

Primary outcome of interest was 30-day readmission rate in adult patients discharged following hospitalisation for an episode of CAP.

Secondary outcomes of interest were; 1) proportion of 30-day readmissions that were a) pneumonia-related, b) pneumonia-unrelated, or c) cardiovascular-related (as a subgroup of pneumonia unrelated, see below); and 2) risk factors for readmission in included studies.

5.2.4 Search Strategy

Comprehensive searches of biomedical electronic databases were conducted: MEDLINE (1946 to September week 4, 2017), EMBASE (1980 to week 40, 2017)), AMED (1985 to October 2017), and Web of Science (1985 to October 2017). The search strategy was designed to include subject headings and key words related to community-acquired pneumonia, hospital readmission, healthcare utilisation and treatment outcome. Only studies published in English were included. Details of the search strategy for each database are detailed in Table 5.1.

The titles, abstracts, and full texts of identified articles were sequentially reviewed and assessed against eligibility criteria. Conference proceedings of the last 3 years for the American Thoracic Society Conference, British Thoracic Society (BTS) Winter Meeting and European Respiratory Society Congress were reviewed to identify potentially eligible articles. Finally, reference lists of included studies were scrutinised to identify potentially relevant articles.

Table 5-1: Search strategy for bibliographic databases

MEDLINE (OVID) & EMBASE (OVID)	AMED (OVID)
1. exp Pneumonia/	1. exp Pneumonia.
2. pneumonia*.mp.	2. pneumonia*.mp.
3. pneumonia*.tw.	3. pneumonia*.tw.
4. exp Community- Acquired Infections/	4. (readmission* or re-admission* or re admission*).mp.
5. community acquired infection*.mp.	5. (readmission* or re-admission* or re admission*).tw.
6. community acquired infection*.tw.	6. (rehospitali#ation* or re-hospitali#ation* or re hospitali#ation*).mp.
7. exp Patient Readmission/	7. (rehospitali#ation* or re-hospitali#ation* or re hospitali#ation*).tw.
8. (readmission* OR re-admission* OR re admission*).mp.	8. OR/1-3
9. (readmission* OR re-admission* OR re admission*).tw.	9. OR/4-7
10. (reattendance* OR re-attendance* OR re attendance*).mp.	10. 8 AND 9
11. (reattendance* OR re-attendance* OR re attendance*).tw.	1. exp Pneumonia.
12. (readmittance* OR re-admittance* OR re admittance*).mp.	2. pneumonia*.mp.
13. (readmittance* OR re-admittance* OR re admittance*).tw.	3. pneumonia*.tw.
14. (rehospitali#ation* OR re-hospitali#ation* OR re hospitali#ation*).mp.	4. (readmission* or re-admission* or re admission*).mp.
15. (rehospitali#ation* OR re-hospitali#ation* OR re hospitali#ation*).tw.	5. (readmission* or re-admission* or re admission*).tw.
16. OR/1-6	
17. OR/7-15	

5.2.5 Data extraction

Study population, methods, outcome measures, and study quality data were independently extracted by two authors (HP, AK, DA, TM) using a pre-designed form (see Appendix 2). The form was initially piloted on five studies and subsequently optimised; any disparity between data extraction by independent authors was resolved by discussion and consensus, including a third reviewer as required.

5.2.6 Assessment of risk of bias

A specific quality assessment tool was created combining relevant aspects from the Newcastle-Ottawa scale and the Down's and Black Quality Assessment Tool.[111,112] This tool was used to assess each study for details pertaining to study period and location, participant selection, and outcome measure with a final total score out of eight (with 0 representing low quality and 8 representing the highest quality rating.)

5.2.7 Data synthesis

Reasons for readmissions were categorised according to pre-defined, hierarchical criteria applied independently by two study authors. Pneumonia-related readmissions included acute or recurrent pulmonary infection (acute onset of signs and symptoms consistent with lower-respiratory tract infection in combination with radiographic features consistent with pneumonia), pleural effusion, empyema, and pulmonary abscess. Pneumonia-unrelated readmissions included any other readmission not fulfilling pneumonia-related readmission criteria. A specific sub-categorisation was specified as cardiovascular-related

readmissions and included coronary artery disease (ischaemic heart disease, angina, myocardial infarction, coronary-artery bypass graft), congestive cardiac failure, cardiomyopathy, tachyarrhythmia, bradyarrhythmia, ruptured abdominal aortic aneurysm, cerebrovascular disease (cerebrovascular accident, transient ischaemic attack), and peripheral vascular disease. This sub-group was pre-specified due to the growing body of evidence indicating an increased risk of cardiovascular events following an episode of CAP.

Random effect meta-analysis was conducted to derive; a) a pooled result of 30-day readmission rate; and b) proportion of pneumonia-related and cardiovascular-related readmissions. The meta-analysis utilised the logit transformation due to its relative simplicity (when compared with arcsine-based transformations) and intuitive interpretation from a practical perspective.

It was anticipated that the identified studies were likely to differ sufficiently in their design, methodology, and populations that subgroups for additional analysis were pre-specified based on; a) study design (retrospective versus prospective), b) study population size (grouped in to studies below and above median population) c) study quality (low quality if score ≤6, high quality if score >6), d) continent of research (Europe versus North America versus Other), e) year of study (year of study beginning enrolment, classified in to studies above and below median study year), and f) type of study (>1000 patients identified through International Classification of Disease (ICD) coding). The cut-off of greater than 1000 patients identified through coding data was employed to differentiate between large administrative datasets, frequently covering several

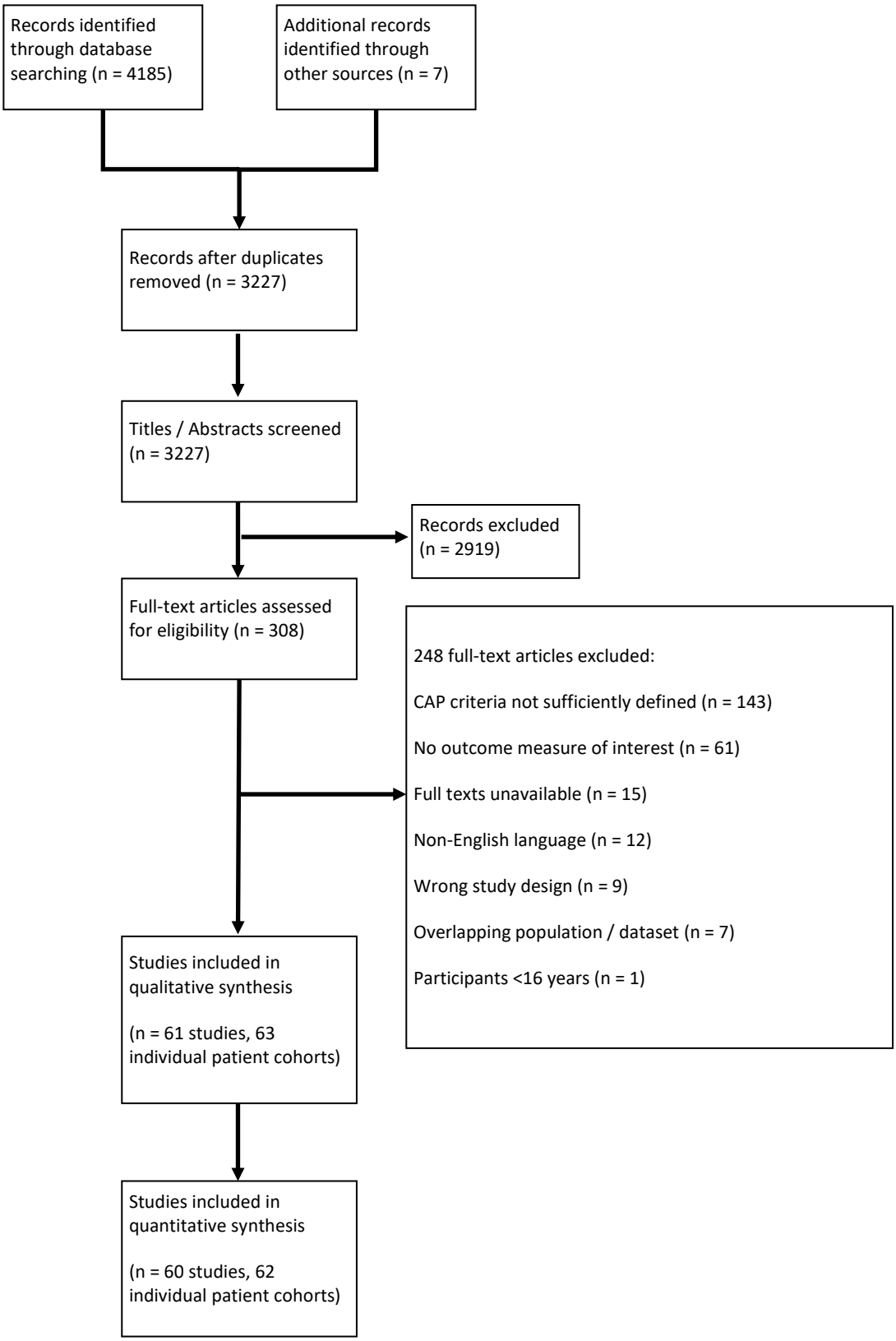
healthcare institutions, and cohort studies which use ICD-10 coding to identify patients within healthcare institutions. Where data was either insufficient or disparate and precluded meta-analysis, qualitative synthesis was conducted to systematically summarise results.

Statistical analysis was conducted using Stata © version 15 (StataCorp. 2017.) The I^2 statistic was used to assist with assessment of heterogeneity between studies.

5.3 Results

The search strategy identified 4185 studies, with 3220 studies remaining after de-duplication (see study flow diagram, Figure 5.1). Seven additional studies were identified from alternate sources. After screening of abstracts and titles 308 studies remained for full text review, with 60 progressing to final synthesis.[48,55,94,95,141-196] Reasons for study exclusion at full-text review included; insufficient methodological detail to ensure patients with HAP excluded (n= 143 studies, 46.4%), no outcome measure of interest (n=61 studies, 19.8%), non-English language (n= 12 studies, 3.9%), and wrong study design (n=9 studies, 2.9%). Full texts were not available for 15 studies (4.9%), seven studies (2.3%) included duplicate populations, and one study enrolled patients from age 14 years.

Figure 5-1: Study flow diagram



5.3.1 Characteristics of included studies

The characteristics of the 60 included studies are summarised in Table 5.2. Briefly, included studies were conducted between 1994 and 2017 providing 62 independent sets of data for analysis (two studies included distinct patient cohorts).[148,180] Europe contributed 28 studies to the review; 18 from Spain, [48,94,95,147-150,153,156,163,166,176,177,183,186,191,192] five from UK, [143,145,160,175,190] two each from Denmark[170,182] and Switzerland, [179,197] and one from the Netherlands.[181] Twenty-nine studies originated from North America, predominantly the US (26 of 29).[55,142,151,157-159,162,164,167,169,171,173,174,180,184,185,187-189,193,194,196,198] Other countries of origin were two studies from Australia,[172,195] a single study each from Japan[165] and Israel,[154] and one international multicentre study.[152]

Mean age of study populations ranged from 44.3 to 81.9 years. Four studies included predominantly (>90%) male participants due to selection criteria (Veterans Association cohorts in North America).[142,157,173,189] Pneumonia severity was most frequently assessed using the Pneumonia Severity Index (PSI) which ranged from 81.2 to 112.5.[147,191] In studies assessing CURB- 65 score, the majority of patients had low or moderate severity CAP (score ≤2).[95,143,145,148,149,179,182,196]

Table 5-2: Summary of Included Studies

Study	Year	Country	Inclusion Criteria	Exclusion criteria	Study Population	30-day readmission rate (%)	Quality Score (/8)
Studies from Europe (28 Studies, 24,368 individual patients)							
Adamuz et al. [48]	2011	Spain	CAP	Immunosuppression: neutropenia, IG deficiency, HIV, transplantation, splenectomy, immunosuppressant medication, corticosteroid therapy, inpatient death	828 patients 65.8% male Mean age 71 / 72 years PSI>90 in 62.2%	8.70	7
Adamuz et al. [95]	2015	Spain	Adults ⩾18 Immunocompetent CAP (LRTI signs and symptoms, radiographic features at X-ray)	Residential care, immunosuppression: neutropenia, immunoglobulin deficiency, HIV, transplantation, splenectomy, immunosuppressant therapy, corticosteroids, cognitive impairment, language barrier	203 patients 61.1% male Mean age 65-72 years CURB65 0-1= 49.4% 2 = 34.3% 3 = 21.3%	11.33	7
Bewick et al. [143]	2010	UK	Adults ⩾ 16 CAP (LRTI signs and symptoms, radiographic features at X-ray)	Hospitalisation in last 10 days, tuberculosis, post-obstructive pneumonia due to lung cancer	397 patients 34.7% male Median age 72 years CURB-65 score 0-1 = 44.3% 2 = 33.2% 3-5 = 22.5%	16.12	5

Study	Year	Country	Inclusion Criteria	Exclusion criteria	Study Population	30-day readmission rate (%)	Quality Score (/8)
Blum et al. [197]	2015	Switzerland	Adults ⩾18 CAP (LRTI signs and symptoms, radiographic features at X-ray, laboratory findings consistent with infection)	Inability to consent IVDU, acute burns, GI bleeding past 90 days, adrenal insufficiency, corticosteroids, pregnancy or breastfeeding, immunosuppression	785 patients 62.0% male Median age 72 years PSI score Class I = 11.7% Class II = 18.0% Class III = 21.1% Class IV = 35.7% Class V = 13.5%	7.64	7
Brettel et al. [145]	2011	UK	CAP (ICD-10 coded with confirmation of consolidation at X-ray)		469 patients 58.8% male Mean age 61 years CURB-65 score 0 = 34.9% 1 = 32.9% 2 = 19.2% ⩾3 = 12.9%	11.73	5
Capelastegui et al. [148] Population A (Baseline cohort)	2005	Spain	Adult ⩾18 CAP (LRTI signs and symptoms, radiographic features at X-ray)	HIV, Immunosuppression, Hospitalised in last 14 days	844 patients 61.3% male Mean age 64.4 & 70.1 years Mean PSI 83.6 & 92.2	2.61	6

Study	Year	Country	Inclusion Criteria	Exclusion criteria	Study Population	30-day readmission rate (%)	Quality Score (/8)
Capelastegui et al.[148] Population B (Follow-up cohort)	2005	Spain	Adult ⩾18 CAP (LRTI signs and symptoms, radiographic features at X-ray)	HIV, Immunosuppression, Hospitalised in last 14 days	654 patients	3.21	6
Capelastegui et al [147] Sub-population	2008	Spain	Adult ⩾18 CAP (LRTI signs and symptoms, radiographic features at X-ray)	Nursing home resident, HIV, Immunosuppression; neutropenia, immunosuppressive medication, corticosteroids, Hospitalised in last 14 days	Unique patients from 2000-2001 not included in Capelastegui 2009; 408 patients	6.60	5.5
Capelastegui et al. [149]	2009	Spain	Adult ⩾18 CAP (LRTI signs and symptoms, radiographic features at X-ray)	Nursing home resident, HIV, Immunosuppression, Hospitalised in last 14 days	1117 patients Mean age 69.4 years Mean PSI 88.9	7.25	7
Carratala et al. [150]	2012	Spain	Adult ⩾18 CAP (LRTI signs and symptoms, radiographic features at X-ray)	ICU admission from ED, imminent death, shock, complicated pleural effusion (empyema or large effusion), pregnancy, aspiration pneumonia, severe social problems	401 patients 64.9% male Mean age 69.7 &71.5 years Mean PSI 100.5 & 101.1	8.23	6.5

Study	Year	Country	Inclusion Criteria	Exclusion criteria	Study Population	30-day readmission rate (%)	Quality Score (/8)
Crisafulli et al. [153]	2013	Spain	Adult ⩾18 CAP (LRTI signs and symptoms, radiographic features at X-ray)	Hospitalised last 14 days HCAP, nosocomial pneumonia, severe immunosuppression, HIV	353 patients 73.9% male Mean age 64.1-72.0 years Mean PSI 86.0-100.4	7.65	6
Falguera et al. [156]	2010	Spain	Clinical diagnosis of CAP PSI risk classes I-III		706 patients	7.37	2
Fleming et al. [160]	2013	UK	CAP		1631 patients	9.63	4
Gordo-Remartinez et al. [163]	2015	Spain	CAP (LRTI signs and symptoms, radiographic features at X-ray) diagnosed in ED	Nosocomial pneumonia (>48h of hospitalisation in the last 30 days), HCAP, baseline co-morbid disease which predisposed to pneumonia	226 patients 55.3% males Median age 75.6 years PSI class I-III (60.6) IV (25.7) V (13.7)	11.50	6
Izquierdo et al. [166]	2010	Spain	Adults ⩾65 years CAP (LRTI signs and symptoms, radiographic features at X-ray)	Institutionalized patients, nosocomial pneumonia	651 patients 62.1% males Median age 77 years PSI score Class I = 0.3% Class II = 6.6& Class III = 29.4% Class IV = 48.6% Class V = 15.1%	10.60	8

Study	Year	Country	Inclusion Criteria	Exclusion criteria	Study Population	30-day readmission rate (%)	Quality Score (/8)
Klausen et al. [170]	2012	Denmark	Age ⩾65 years WHO ICD-9 coded for pneumonia	pulmonary mycosis, viral pneumonia	10019 patients 50.2% males Age group 65-74 = 32.5% 75-84 = 40.6% ⩾85 = 26.9%	12.28	8
Maqsood et al. [175]	2013	UK	CAP (LRTI signs and symptoms, radiographic features at X-ray) Follow-up with community respiratory assessment services (RAS)		67 patients CURB-65 score 0-1 = 48% 2 = 27% ⩾3 = 25%	8.96	3
Marcos et al. [177]	2013	Spain	Age ⩾18 CAP (LRTI signs and symptoms, radiographic features at X-ray) PSI score class I or II	HCAP, PSI score class ⩾III	65 patients 66.2% male Mean age 44.3 & 44.7 years	3.10	6
Marcos et al. [176]	2017	Spain	Age ⩾18 CAP (LRTI signs and symptoms, radiographic features at X-ray) PSI I or II	HCAP, admission for palliative care	155 patients 56.1% males Median age 45 years Median PSI score 53	1.94	6

Study	Year	Country	Inclusion Criteria	Exclusion criteria	Study Population	30-day readmission rate (%)	Quality Score (/8)
Marti et al. [179]	2017	Switzerland	CAP (LRTI signs and symptoms, radiographic features at X-ray)	Severe CAP (PSI score V, immediate ICU admission, fulfilling ⩾3 minor criteria on ATS rule), immunosuppression, nursing home residence,	371 patients 43.9% male Mean age 76 years CURB-65 Score 0 = 13.5% 1 = 34.8% 2 = 37.7% ⩾3 = 14.0%	7.73	5
Meijvis et al. [181]	2011	Netherlands	Age ⩾18 CAP (LRTI signs and symptoms, radiographic features at X-ray)	Immunocompromise; congenital or acquired immunodeficiency, chemotherapy or corticosteroids or immunosuppressive treatment last 6 weeks, haematological malignancy, immediate ICU, pregnancy, breast feeding	304 patients 56.3% males Mean age 62.8 & 64.5 years, Mean PSI 95.8 & 100.2	4.61	7
Melgaard et al. [182]	2017	Denmark	Age ⩾18 CAP (LRTI signs and symptoms, radiographic features at X-ray)	ICU transfer, impaired cognition	154 patients 57.1% males Mean age 77.4 years CURB-65 score 0 = 5.2% 1 = 24.7% 2 = 44.8% 3 = 15.6% 4 = 3.9% 5 = 0.6%	17.01	5.5

Study	Year	Country	Inclusion Criteria	Exclusion criteria	Study Population	30-day readmission rate (%)	Quality Score (/8)
Menendez et al. [183]	2007	Spain	Age ⩾16 CAP (LRTI signs and symptoms, radiographic features at X-ray)	Hospitalisation in last 10 days, admission to ICU, immunosuppression due to medication, HIV, broncho-aspiration, active tuberculosis	271 patients 40.6% males Mean age 69.4 & 72.3 years	6.22	6.5
Reyes-Calzada et al. [186]	2007	Spain	Age ⩾18 CAP (LRTI signs and symptoms, radiographic features at X-ray)	HIV, transplantation, immunosuppressive treatment including corticosteroids, lung abscesses, active tuberculosis, suspected aspiration, hospitalisation in last 15 days	425 patients 65% males Mean age 69 years PSI score Class I = 7.3% Class II = 12.2% Class III = 21.9% Class IV = 40.0% Class V = 18.6%	8.21	6
Taylor et al. [190]	2013	UK	CAP (LRTI signs and symptoms, radiographic features at X-ray)	Age <18 years, HAP, active malignancy of the thorax, immunosuppressed, palliative care	1223 patients 59.9% males Mean age 66.0 & 74.0 years	11.20	7
Torres et al. [191]	2004	Spain	CAP (LRTI signs and symptoms, radiographic features at X-ray)	Hospitalisation in last 15 days, nursing home residents, final diagnosis other than CAP, pulmonary metastasis	75 patients 74.7 % male Mean age 79.2 years Median age 77.8 years Mean PSI 106.9	15.71	5

Study	Year	Country	Inclusion Criteria	Exclusion criteria	Study Population	30-day readmission rate (%)	Quality Score (/8)
Uranga et al. [94]	2016	Spain	Age ⩾18 CAP (LRTI signs and symptoms, radiographic features at X-ray)	HIV, chronic immunosuppression, splenectomy, immunosuppressive treatment, neutropenia, nursing home resident/ discharge from acute care hospital or onsite subacute care unit or palliative care unit in last 14 days, antibiotics in last 30 days, extra pulmonary infection, meningitis, endocarditis	283 patients 69.3% males Mean age 64.7 & 66.2 years Mean PSI 81.8 & 83.7	3.89	7
Viasus et al. [192]	2017	Spain	CAP (LRTI signs and symptoms, radiographic features at X-ray) Streptococcus Pneumoniae aetiology (1⩾ culture positive for S. pneumoniae) Admitted via ED	Inpatient death in first 72hours, Antibiotic treatment with penicillin / amoxicillin / co-amoxiclav preceding admission	1283 patients 62.8% males Median age 69 & 69.5 years PSI class IV-V 65% & 83%	2.73	6

Study	Year	Country	Inclusion Criteria	Exclusion criteria	Study Population	30-day readmission rate (%)	Quality Score (/8)
Studies from North America (30 Studies, 139,357 individual patients)							
Akhtar et al. [141]	2015	USA	CAP or HCAP Thoracic imaging with infiltrate and appropriate clinical picture		156 patients Mean age 57-67 years	17.76	2
Barakat et al. [142]	2015	USA	Age ⩾50 ICD-9 coded pneumonia	Hospitalisation within 90 days Pneumonia secondary to *Pneumocystis jiroveci, Mycobacterium tuberculosis,* or fungal infection, female gender, undetermined HIV status	1203 patients 100% male Median age 56-57 years	12.55	5.5
Cabrera et al. [146]	2013	USA	CAP diagnosis identified through medical records review		454 patients	18.50	2
Chew et al. [151]	2011	USA	Adult ⩾18 HIV positive and CAP (WHO ICD-9 code for pneumonia and HIV)	HIV negative, hospitalised in last 10 days, tuberculosis, pneumocystis pneumonia, no radiographic evidence pneumonia within 48 hours admission, not treated as CAP, inter-hospital transfer	102 patients 69.6% male Mean age 45.4 years PSI score Class I = 18.6% Class II- = 38.2% Class III = 24.5% Class IV = 14.7% Class V = 3.9%	15.69	5

Study	Year	Country	Inclusion Criteria	Exclusion criteria	Study Population	30-day readmission rate (%)	Quality Score (/8)
Dean et al. [155]	2006	USA	Adult ⩾66 years WHO ICD-9 code for respiratory failure or sepsis with secondary code pneumonia	Hospitalised in last 10 days, LOS < 1day, self-discharge, HIV, organ transplantation, hospitalised with a diagnosis of pneumonia in last 60 days	7942 patients 44.8% males Mean age 72.3 years	10.20 & 11.70	6
Feldman et al. [157]	2003	USA	Adult ⩾18 Admitted to general medical ward and had documented WHO ICD-9 code for CAP CAP (LRTI signs and symptoms, radiographic features at X-ray)	Presumed HAP Immunosuppression: HIV, neutropenic or immunosuppressed Mycobacterial infection	442 patients 95.7% male Mean age 98 years Mean PSI 85.5-104.6	10.41	4
Fishbane et al. [158]	2007	USA	CAP (LRTI signs and symptoms, radiographic features at X-ray)	Hospitalisation in last 30 days, immediate ICU admission, active immunosuppression, AIDS, active malignancy, cystic fibrosis, patient refusal of active treatment	344 patients 50.0% male Mean age 73.5 years Mean PSI 88.9	5.23	5.5
Flanders et al. [159]	2006	USA	Adult ⩾18 CAP (clinical diagnosis of with CXR within 48 hrs admission demonstrating an acute infiltrate)	Hospitalisation in last 10 days, HIV, history of organ transplant or use of immunosuppressive therapy, cystic fibrosis, post obstructive pneumonia, active tuberculosis	318 patients Median age 74.0-76.0 years Median PSI score 97-108	11.95	5.5

Study	Year	Country	Inclusion Criteria	Exclusion criteria	Study Population	30-day readmission rate (%)	Quality Score (/8)
Gilbert et al. [161]	1998	USA	Adult ⩾18 CAP (LRTI signs & symptoms, radiographic features at X-ray)	Hospitalisation in last 10 days HIV, no antimicrobial therapy, or details of therapy unavailable	1178 patients 52.2% male Mean age 64.3 years	10.19	6.5
Godar et al. [162]	2011	USA	Adult > 17 years CAP (LRTI signs and symptoms, radiographic features at X-ray within 6 hours of presentation) ⩾1 fasting glucose measure within 6 hours of presentation	Antibiotics for LRTI in last 3 weeks ICU admission or transfer within 12 hours transferred from another hospital, self-discharge, hospitalisation in last 30 days. History of or suspected: aspiration, fungal, or viral pneumonia Pulmonary tuberculosis or *Pneumocystic carinii* pneumonia within 1 year prior to admission/ AIDS, HIV, or tracheostomy	969 patients 56.1% males Mean age 73.8 years PSI score ⩾91 = 3.6% <91 = 96.4%	7.95	5.5
Halm et al. [55]	2002	USA	Adult ⩾ 18 CAP (LRTI signs and symptoms, radiographic features at X-ray)	Immunodeficiency, hospitalised in last 10 days	680 patients 51.3% males Mean age 57.9 years PSI score Class I = 21.7% Class II = 27.5% Class III = 22.2% Class IV = 20.3% Class V = 8.2%	9.85	7.5

Study	Year	Country	Inclusion Criteria	Exclusion criteria	Study Population	30-day readmission rate (%)	Quality Score (/8)
Houck et al. [164]	2004	USA	Adult ⩾65 years WHO ICD-9 code for pneumonia	Lack of antibiotic timing data or radiographic evidence of pneumonia in medical records, / Immunocompromised, lack of antibiotic treatment during the first 36h at the hospital, discharge, or death on the day of admission, hospitalisation in Puerto Rico or Virgin Islands, hospitalisation in the last 14 days	12807 patients 51.8% males Age groups: 65-74 = 27.3% 75-84 = 41.8% ⩾85 = 30.9% PSI score: Class II = 6.8% Class III = 22.2% Class IV = 46.8% Class V = 24.2%	13.40	7.5
Hueston et al. [198]	1994	USA	Adult >18 CAP determined from discharge abstracts	Inter-hospital transfer, nosocomial pneumonia, immunosuppressive medication, neutropenia, HIV	157 patients Mean age 66.4 & 73.1 years	11.46	5
Jasti et al. [167]	2008	USA	Clinical diagnosis CAP Treated for CAP Radiographic evidence of CAP	Age <18 years Hospitalisation in last 10 days Cystic fibrosis, active pulmonary TB, alcohol abuse with organ dysfunction, illicit drug use, palliative care, homelessness, inpatient less than 24 hours, immunosuppression, AIDS, HIV, MRSA positive	577 patients 45.6% males Median age 71 years PSI score Class I = 10.7% Class II = 33.0% Class III = 33.8% Class IV = 33.1% Class V = 13.3%	12.13	8

Study	Year	Country	Inclusion Criteria	Exclusion criteria	Study Population	30-day readmission rate (%)	Quality Score (/8)
Johnstone et al. [168]	2008	Canada	Age ⩾17 Signs and symptoms of LRTI Radiographic evidence of CAP	active TB, cystic fibrosis, pregnancy	2950 patients 58.5% males Mean age 68.9 years PSI score Class I-II = 19% Class III = 19% Class IV = 40% Class V = 23%	2.24	7
Kim et al. [169]	2015	USA	Age ⩾65 years WHO ICD-9 coded for pneumonia, functional decline between hospital admission and 48 hours since hospital admission	LOS 2 days or less, HCAP, data missing during matching process, inpatient death deceased in the hospital	1058 patients 39.8% males Median age 86.2 & 94.2 years	13.80	6
Lee et al. [171]	2011	USA	Age ⩾18 CAP (LRTI signs and symptoms, radiographic features at X-ray)	HAP, immunosuppression, cystic fibrosis, pregnancy, psychosocial conditions, substance abuse	2076 patients 48.8% males Median age 74 years PSI class I = 7.6% II = 19.5% III = 24.4% IV = 37.5% V = 11.0%	8.43	6

Study	Year	Country	Inclusion Criteria	Exclusion criteria	Study Population	30-day readmission rate (%)	Quality Score (/8)
Madaras-Kelly et al. [173]	2016	USA	WHO ICD-9 code for pneumonia, Admission to any medical ward including ICU for ⩾ 48h, ⩾24h inpatient antimicrobial therapy	Complicated pneumonia, necrotising pneumonia, thoracentesis, significant immunosuppression, extra pulmonary infection, inter-hospital transfer, pneumonia occurred >48h after admission or discharged without documentation of completing full course therapy, gram negative non-fermentative bacilli, inpatient death	1739 patients 96.6% males Mean age 71.8 years PSI score Class I = 1.8% Class II = 11.4% Class III = 20.1% Class IV = 43.6% Class V = 23.2%	12.94	6
Mansouri et al. [174]	2011	USA	WHO ICD-9 code for pneumonia, Case notes review for clinical diagnosis of CAP (Signs and symptoms of LRTI, radiology reported thoracic imaging with evidence of CAP)	Antibiotic treatment pre-admission (within last 30-days), HAP or HCAP, ICU admission	130 patients 96.2% males Mean age 66.7 & 69.7 years	11.54	4.5
Marrie et al. [178]	2004	Canada	WHO ICD-9 code for pneumonia	Not resident in Alberta, treated outside Alberta care facility, hospitalisation for surgical procedure, hospitalisation in last 10 days	4268 patients 50.7% male Mean age 53.5 & 53.7 years	17.99	6

Study	Year	Country	Inclusion Criteria	Exclusion criteria	Study Population	30-day readmission rate (%)	Quality Score (/8)
Meehan et al. [180] Population A	2001	USA	WHO ICD-9 code for pneumonia Case notes review for clinical diagnosis of CAP Radiographic evidence of CAP	Age <65 years, hospitalisation in last 10 days, HIV, organ transplant, chemotherapy in last 2 months, inter-hospital transfer, ICU admission within 24 hours of admission, inpatient death within 24 hours of admission	1242 patients 47.0% males Mean age 81.9 years	13.12	6
Meehan et al. [180] Population B	2001	USA	WHO ICD-9 code for pneumonia Case notes review for clinical diagnosis of CAP Radiographic evidence of CAP	Age <65 years, hospitalisation in last 10-days, HIV, organ transplant, chemotherapy in last 2 months, inter-hospital transfer, ICU admission within 24 hours of admission, inpatient death within 24 hours of admission	1146 patients 48.1% males Mean age 80.5 years	15.01	6
Metersky et al. [184]	2000	USA	Age >65 WHO ICD-9 code for pneumonia, respiratory failure, sepsis (primary and/or secondary code)	Hospitalisation in last 10 days, inter-hospital transfer, HIV, organ transplant, discharge on date of hospital admission, self-discharge	34441 patients 53.4% males	3.42	6
Micek et al. [185]	2014	USA	CAP (LRTI signs and symptoms, radiographic features at X-ray) Treated in ED with regime that included ceftriaxone plus azithromycin moxifloxacin	HAP	259 patients 57.5% males Mean age 58.1 & 62.0 years	15.44	7

Study	Year	Country	Inclusion Criteria	Exclusion criteria	Study Population	30-day readmission rate (%)	Quality Score (/8)
Shrestha et al. [187]	2016	USA	CAP (LRTI signs and symptoms, radiographic features at X-ray)		77 patients	10.39	2
Stone et al. [188]	2005	USA	Age ⩾18 CAP (LRTI signs and symptoms, radiographic features at X-ray)	PSI class V, mechanical ventilation, active underlying pulmonary disease, serious co-morbid illness, critical care admission, immunocompromise, admission for palliative care, nursing home residence, homelessness, pregnancy, nursing, or of childbearing potential, illicit drug use, hospitalisation in last 10 days. Pneumonia with hospitalisation in last 30 days, allergy to cephalosporin or penicillin	449 patients 48.8% male, Age > 65years = 54.6% PSI score Class I = 15.6% Class II = 29.0% Class III = 26.1% Class IV = 29.4%	8.02	7
Tang et al. [189]	2014	USA	Age ⩾65 WHO ICD-9 primary code pneumonia or influenzae, or primary code of respiratory failure or sepsis with secondary code pneumonia	Inpatient death, patients admitted to hospital with less than 25 CAP admission per year	45134 patients 98% males Mean age 77 years	13.20	5

Study	Year	Country	Inclusion Criteria	Exclusion criteria	Study Population	30-day readmission rate (%)	Quality Score (/8)
Walsh et al. [193]	2016	USA	WHO ICD-9 code for pneumonia	Age <18 Inter-hospital transfer, self-discharge, inpatient death, extra-pulmonary infection requiring treatment, neutropenia, immunodeficiency, any healthcare exposure in last 90 days	97 patients 46.4% male Mean age 65 years	14.43	6
Whittle et al. [194]	1998	USA	WHO ICD-9 code for pneumonia	Hospitalised in last 10 days, AIDS, organ transplant, code for multiple trauma or elective surgical procedures performed on the first 2 hospital days	17180 patients 61.1% male	15.80	6
Zasowski et al. [196]	2014	USA	Age ⩾18 CAP (LRTI signs and symptoms, radiographic features at X-ray) Treated with ceftriaxone and azithromycin on admission and for at least 24 hours PSI class III or IV	PSI I, II, and V, pathogen resistant to ceftriaxone, previous antimicrobial therapy for CAP for ⩾ 24 hours in 96 hours prior to hospital admissions, systemic corticosteroids, haematological disease, immunological disease, pregnancy, breast feeding	236 patients 62.7% male Mean age 65.9 years, PSI score Class III = 41% Class IV = 59%	12.29	7

Study	Year	Country	Inclusion Criteria	Exclusion criteria	Study Population	30-day readmission rate (%)	Quality Score (/8)
Studies from Other (5 Studies, 2,714 individual patients)							
Chirino et al. [152]	2014	Multi-national	CAP with clinical stability within 5 days after admission		1200 patients 89.3% males Median age 65.0 years	11.00	3
Dagan et al. [154]	2006	Israel	Adult ⩾18 CAP (LRTI signs and symptoms, radiographic features at X-ray)		373 patients 53.9% males Mean age 63.4 years PSI score Class I = 14.7% Class II = 14.2% Class III = 15.8% Class IV = 33.8% Class V = 21.4%	7.51	4
Ishida et al. [165]	2017	Japan	Adult > 16 CAP (LRTI signs and symptoms, radiographic features at X-ray)	Nursing home residents with immunocompromise, HAP, previous use of corticosteroids, immunosuppressive therapy, active neoplasm, HIV, acute tuberculosis	705 patients 65.7% males Mean age 74.5 & 78.8 years	3.40	4.5

Study	Year	Country	Inclusion Criteria	Exclusion criteria	Study Population	30-day readmission rate (%)	Quality Score (/8)
Lee et al.[172]	2007	Australia	Signs and symptoms of LRTI Radiographic evidence of CAP	hospitalisation in last 14days, immunosuppression	225 patients 56.4% Males Mean age 71.2 & 72.0 years PSI Score Class I = 4.9% Class II = 12.0% Class III = 22.2% Class IV = 33.3% Class V = 27.6%	6.10	4
Yaw et al.[195]	2016	Australia	CAP (LRTI signs and symptoms, radiographic features at X-ray)		211	11.85	3

5.3.2 Risk of bias in included studies

Across all included studies the median quality score was 6 (range 2 to 8). Sixteen studies were categorised as high quality (score ≥7). Quality score was most frequently reduced by not reporting loss to follow-up (68%), funding source (83%), or conflicts of interest (77%).

5.3.3 Pooled estimate of 30-day readmission rate

The pooled estimates for 30-day readmission rate in adult patients discharged following hospitalisation with radiographically confirmed CAP was 0.10 (95% Confidence Interval (CI) 0.08-0.11, I^2=99.0%) (Table 5.3, Figure 5.2).

5.3.3.1 Subgroup Analysis

Retrospective studies had significantly higher 30-day readmission rates compared to prospective studies, 0.12 (95% CI 0.10-0.14, I2=99.5%) versus 0.08 (95% CI 0.06-0.09, I^2=93.5%), p value <0.001. (Table 5.3, Figure 5.3). Considering continent of study origin, 30-day readmission rate was significantly higher in North America (0.12, 95% CI 0.09-0.14, I^2=99.5%) compared to Europe (0.08, 95% CI 0.06-0.10, I^2=95.3%) and 'other' (0.08, 95% CI 0.04-0.12, I^2=92.3%) (Table 5.3, Figure 5.4).

Subgroup analysis examining study type (large 'database' studies with >1000 participants and using WHO ICD10 coding versus other studies) demonstrated a significantly higher 30-day readmission rate in large database studies (0.13, 95% CI 0.09-0.17, I^2 = 93.3%) compared to other studies (0.09, 95% CI 0.08-0.10, I^2=99.8%) (Table 5.3,) Of the large 'database' studies, Metersky et al (n=34,441 participants) reported a substantially lower readmission rate of 3% compared to

all the other large database studies (mean 13%). No other significant associations were identified in the pre-specified subgroup analyses (Table 5.3). Furthermore, none of the pre-specified subgroups could explain the high levels of heterogeneity observed.

Table 5-3: Summary of pooled estimates from random effects meta-analyses of included studies, by exposure (subgroups)

Exposure	Number of Studies (n)	Pooled estimates	95% Confidence Intervals	I^2 (%)
All studies	62	0.10	0.08-0.11	99.0
Retrospective studies	29	0.12	0.10-0.14	99.5
Prospective studies	33	0.08	0.06-0.09	93.5
North America	29	0.12	0.09-0.14	99.5
Europe	28	0.08	0.06-0.10	95.3
'Other' countries	5	0.08	0.04-0.12	92.3
Large Database studies	11	0.13	0.09-0.17	93.3
Representative studies	46	0.10	0.06-0.12	97.7
Non-representative studies	16	0.09	0.06-0.13	99.6
High Quality (⩾7)	16	0.09	0.07-0.12	95.5
Low Quality (⩽6)	46	0.10	0.06-0.12	99.1
Population above Median (>451 participants)	31	0.10	0.06-0.12	99.5
Population below Median (<451 participants)	31	0.09	0.06-0.11	75.4

Figure 5-2: Random effects meta-analysis of 30-day readmission rate for adult patients discharged from hospital following an episode of Community-Acquired Pneumonia

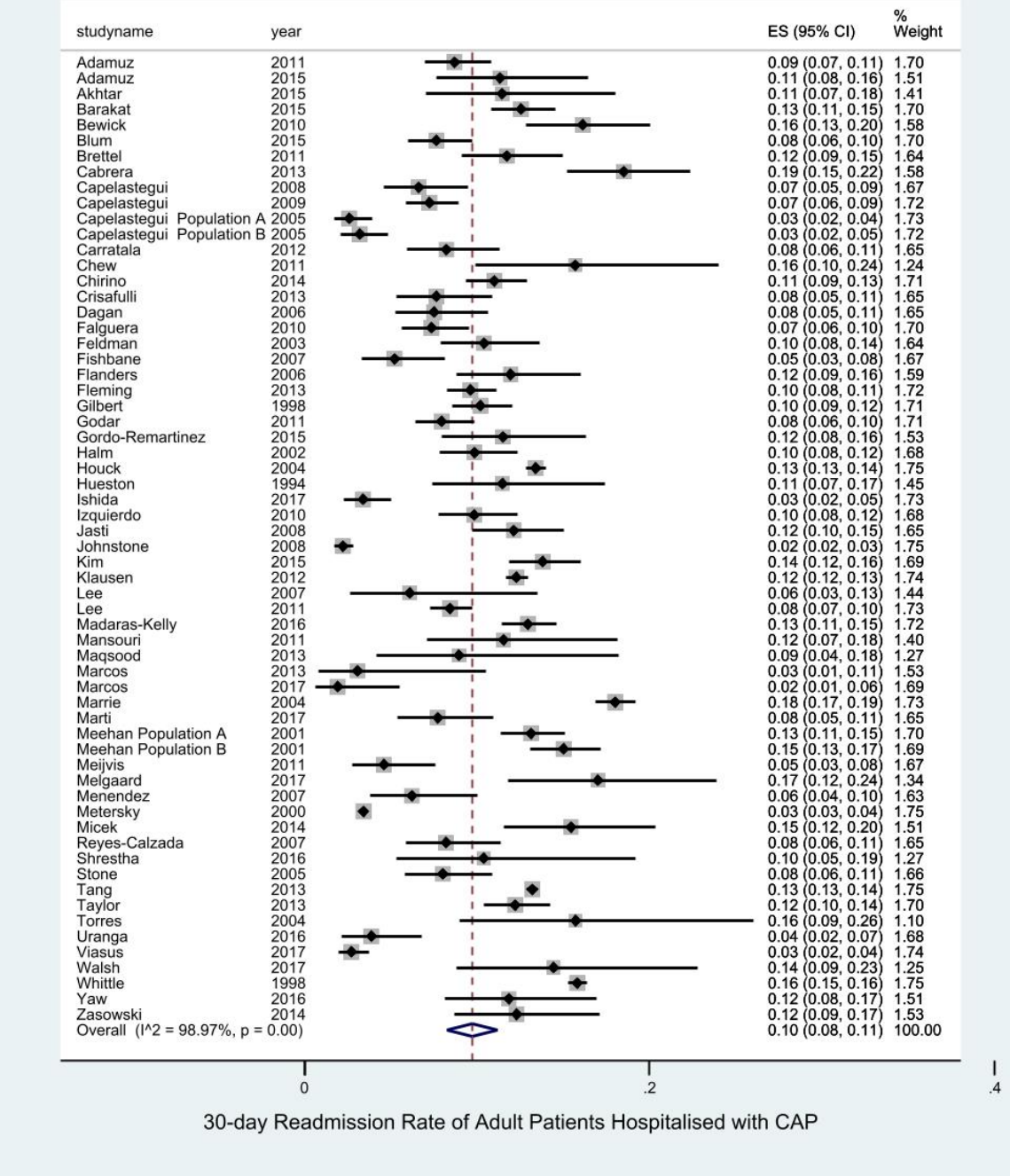


Figure 5-3; Random effects meta-analysis of 30-day readmission rate for adult patients discharged from hospital following an episode of Community-Acquired Pneumonia categorised by retrospective versus prospective study design

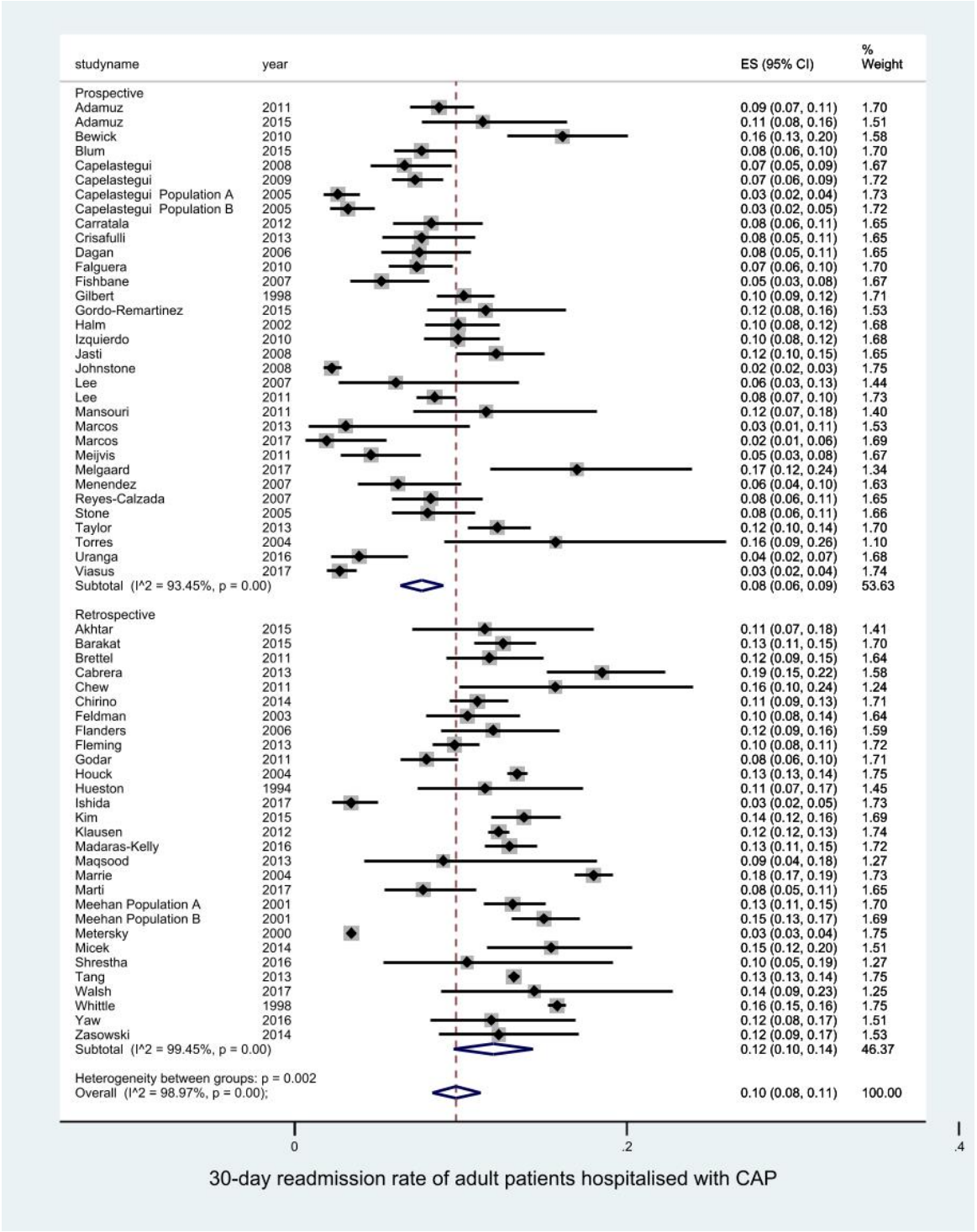
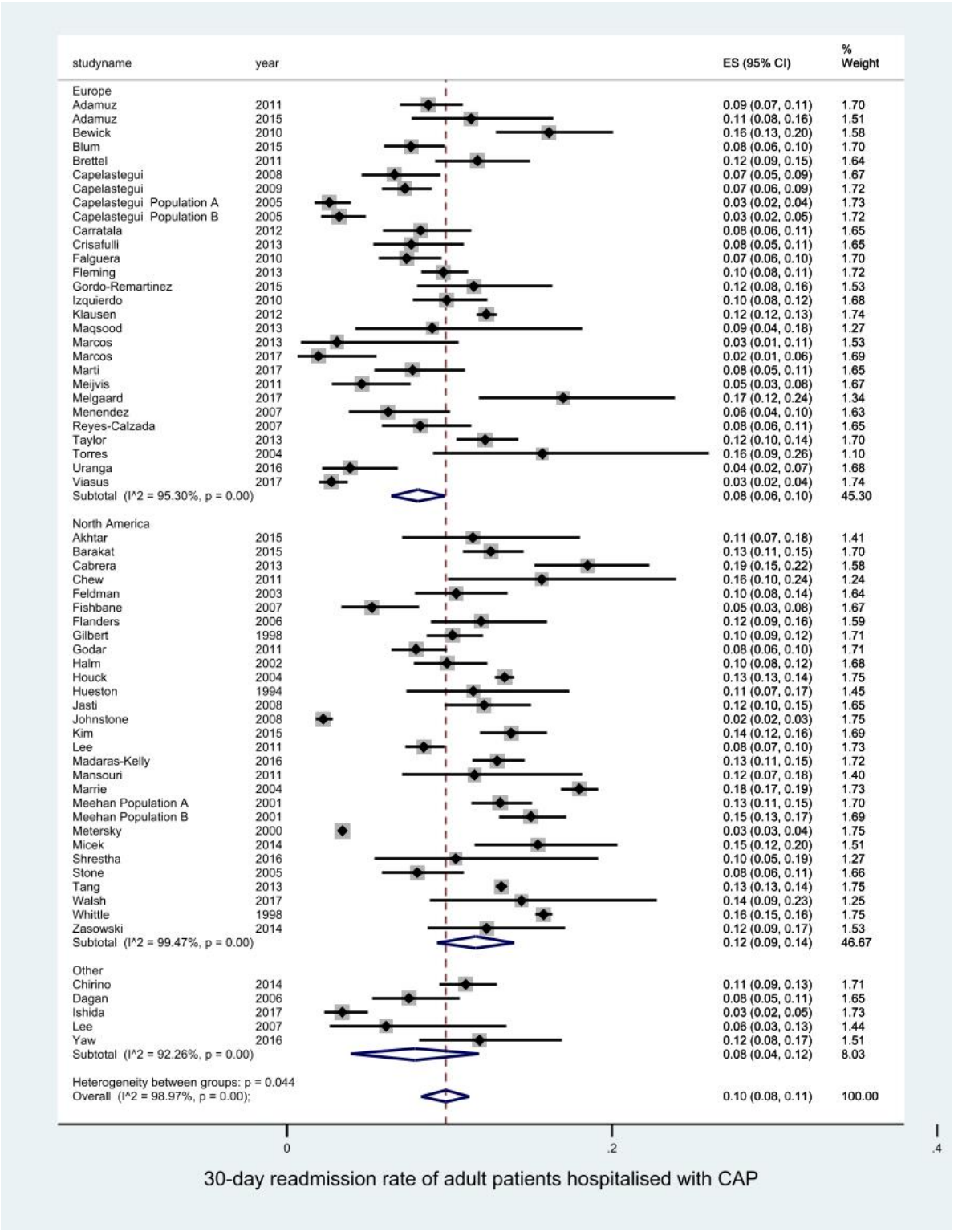


Figure 5-4: Random effects meta-analysis of 30-day readmission rate for adult patients discharged from hospital following an episode of Community-Acquired Pneumonia categorised by continent of study



5.3.4 Reason for 30-day readmission

In the studies which classified cause of 30-day readmission, 32% (95% CI 0.25-0.37, I^2=69.8%) were classified as pneumonia-related (11 studies, 9,216 patients) (Figure 5.6).[48,145,149,150,156,157,167,178,193,196]

Data were available for further categorisation in to a cardiovascular-related readmission in four studies (n=2,923 patients). In these studies, 20% (95% CI 0.14-0.26, I^2=33.6%) of all 30-day readmission following CAP were categorised as cardiovascular-related (Figure 5.7).

Figure 5-6: Random effects meta-analysis of proportion of pneumonia-related 30-day readmissions in adult patients discharged from hospital following an episode of Community-Acquired Pneumonia

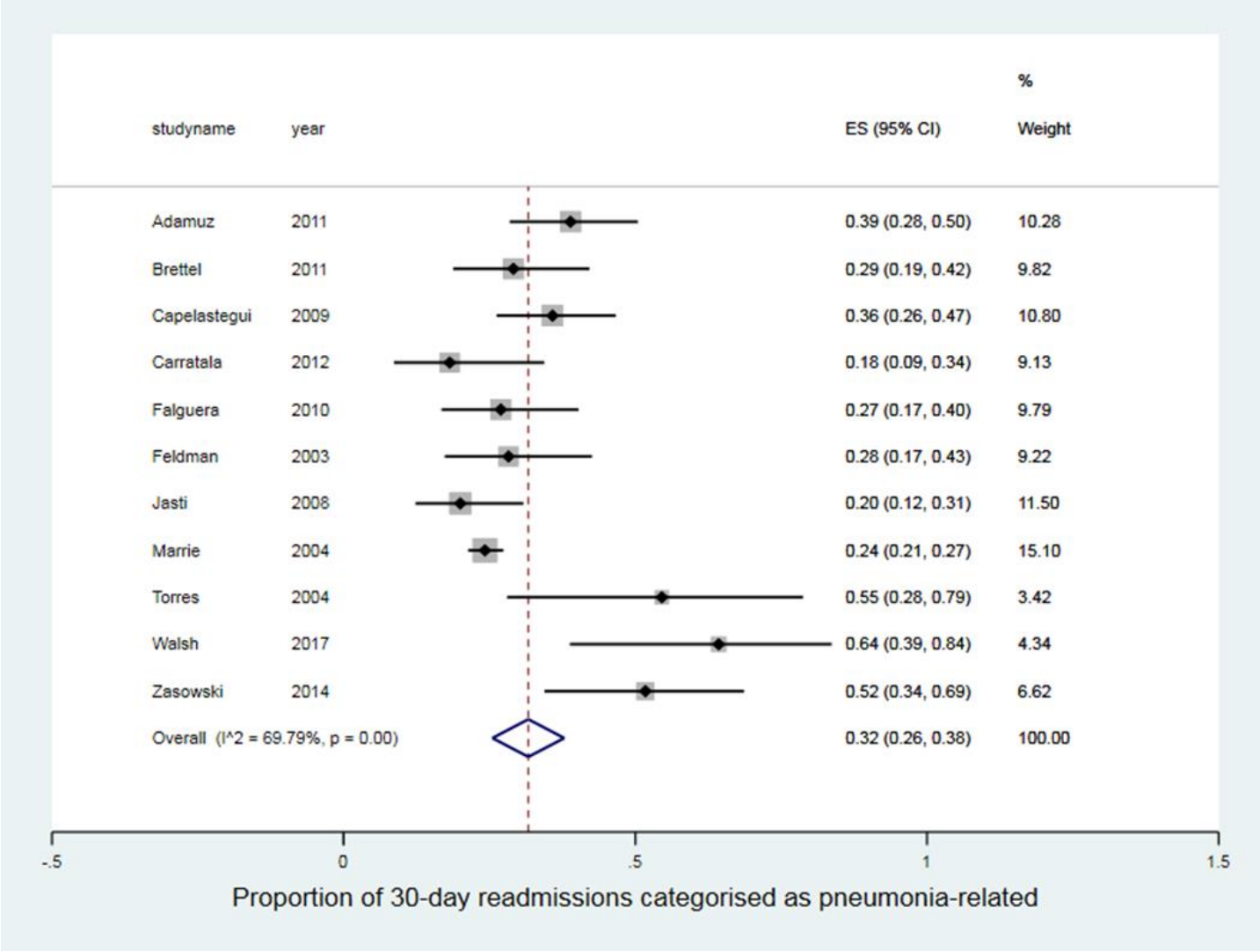
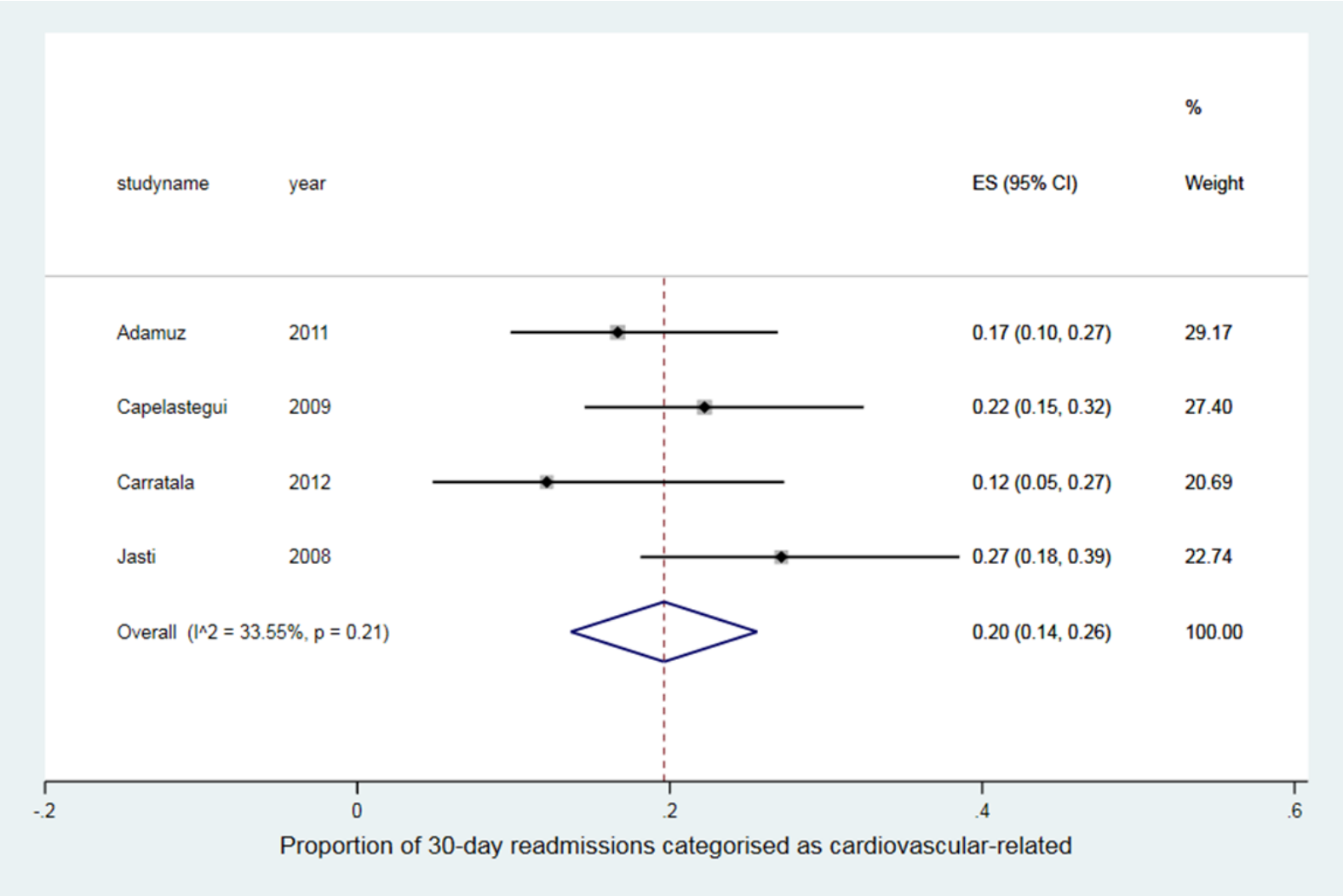


Figure 5-7: Random effects meta-analysis of proportion of cardiovascular-related 30-day readmissions in adult patients discharged from hospital following an episode of Community-Acquired Pneumonia



5.3.5 Risk factors for readmission

Risk factors for 30-day readmission were reported in 13 studies and are summarised in Table5.4. The risk factors assessed, and outcome measures employed varied substantially between studies such that quantitative synthesis was not appropriate. Qualitative summation is outlined below.

5.3.5.1 Pre-admission factors

Increasing co-morbid illness, measured either as increasing number of illnesses or as Charlson index, was significantly associated with an increased 30-day readmission rate in 3 of 5 studies,[166,170,178] whereas increasing age was only associated with increased readmission in one of 5 studies.[189] Isolated studies identified specific comorbid illnesses as being significantly associated with increased readmission; Chronic Obstructive Pulmonary Disease (COPD, aOR 2.3, n=1 study),[167] Congestive Cardiac Failure (CCF, aOR 1.18, n=1 study),[189] coronary artery disease (aOR2.7, n=1 study),[167] Acquired immunodeficiency syndrome (AIDS, aOR 1.99, n=1 study),[189] peptic ulcer disease (aOR 1.24, n=1 study),[189] and chronic kidney disease (CKD, aOR 1.18, n=1 study).[167]

One study identified a significant association between markers of socio-economic status and an increased risk of 30-day readmission; unemployment (aOR 3.7, 95% CI 1.1 – 12.3), and less than high-school education (aOR 2.0, 95% CI 1.1 – 3.4).[167] Frequent healthcare utilisation prior to the index admission was also significantly associated with increased readmissions in 4 of 4 studies; hospital admission in the last 90 days (aOR 1.6 and 2.47, n=2 studies), [48,189] emergency department attendance in last 12 months (aOR 1.04, n=1 study), [189] and antibiotics in previous 30 days (aOR 2.12, n=1 study).[185]

5.3.5.2 Factors at the time of hospital admission and discharge

Severity of CAP on admission was not associated with increased risk of 30-day readmission in four of five studies.[48,145,167,185,196] None of the studies measuring process of care measures at the time of admission observed an association with 30-day readmission rate.[145,164,173]

One US study (n=680 participants, readmission rate 9.85%) observed a significant association between the number of pre-defined 'clinical instabilities' at discharge and the risk of 30-day readmission (1 instability and 2 or more instabilities versus no instabilities, aOR 1.3 (95% CI 0.7-2.5) and aOR 3.5 (95% CI 1.0-12.4), p value for trend <0.02).[55] A later European study (n=828 participants, readmission rate 8.70%) found no significant association between 'stability at discharge' and readmission rate (OR 1.8, 95% CI 0.41 o 7.93).[48]

Table 5-4: Risk factors for readmission at 30-days following hospitalisation with CAP.

a) Pre-admission risk factors

	Risk Factor	Study	Outcome measure	p value
Intrinsic				
Sex	Male	Klausen 2012	HR 1.36 (1.21-1.52)	<0.01
		Whittle 1998	aOR 1.21 (1.11-1.32)	not reported
		Zasowski 2014	RR 0.69 (0.35-1.36)	non-significant
Age	Per year increase age	Brettel 2011	OR 0.995 (0.959-1.033)	not reported
		Tang 2014	aOR 1.01 (1.00-1.02)	<0.01
	45-64 years	Jasti 2008	aOR 3.2 (0.4-26.7)	non-significant
	>65 years		aOR 2.7 (0.3-21.6)	non-significant
	>65 years	Adamuz 2011	aOR 1.43 (0.66-3.01)	0.37
		Zasowski 2014	RR 0.59 (0.29-1.17)	non-significant
	65-69 years	Whittle 1998	reference	not reported
	70-74 years		aOR 1.05 (0.91-1.22)	not reported
	75-79 years		aOR 0.95 (0.81-1.10)	not reported
	80-84 years		aOR 1.14 (0.98-1.32)	not reported
	>85 years		aOR 1.05 (0.91-1.22)	not reported
	65-74 years	Klausen 2012	reference	
	75-84 years		HR 1.09 (0.96-1.24)	non-significant
	>85 years		HR 1.04 (0.89-1.21)	non-significant
Ethnicity	First Nations Aboriginals	Marrie 2004	aOR 1.42 (1.21-1.68)	<0.05
	Non-White	Tang 2014	reference	
	White		aOR 1.14 (1.02-1.28)	0.02
	Hispanic		aOR 1.26 (1.07-1.47)	0.01
	Black versus White	Whittle 1998	aOR 1.25 (1.09-1.49)	not reported
	Black	Zasowksi 2014	RR 1.16 (0.47-2.84)	non-significant

	Risk Factor	Study	Outcome measure	p value
Extrinsic				
Social Factors	Unemployed	Jasti 2008	aOR 3.7 (1.1-12.3)	<0.05
	Less than high school education	Jasti 2008	aOR 2.0 (1.1-3.4)	<0.05
	Nursing home residency	Tang 2014	aOR 1.68 (1.18-2.39)	<0.01
Pre-hospital management	Pneumococcal vaccination	Adamuz 2011	aOR 1.83 (0.92-3.63)	0.08
	Influenzae vaccination	Adamuz 2011	aOR 1.16 (0.53-2.55)	0.71
	Antibiotics last 30 days	Micek 2014	OR 2.12 (1.45-3.10)	<0.05
	Oral corticosteroids last 90 days	Tang 2014	OR 1.16 (1.06-1.27)	<0.01
	Hospital admission last 90 days	Adamuz 2011	aOR 2.47 (1.11-5.52)	<0.05
		Tang 2014	aOR 1.60 (1.46-1.75)	<0.01
	CAP last 180 days	Zasowski 2014	RR 0.43 (0.06-3.0)	non-significant
	ED attendance last 12 months	Tang 2014	OR 1.04 (1.02-1.06)	<0.01
Co-morbidity	Charlson Index	Brettel 2011	OR 1.08 (0.78-1.49)	not reported
	Charlson Index 0	Klausenl 2012	reference	
	Charlson Index 1		HR 1.21 (1.06-1.39)	<0.01
	Charlson Index 2		HR 2.27 (1.95-2.64)	<0.01
	Charlson Index 3		HR 2.8 (2.17-3.61)	<0.01
	Charlson Index 4		HR 3.3 (2.47-4.41)	<0.01
	any co-morbid disease	Brettel 2011	OR 2.045 (0.415-10.89)	not reported
	any co-morbid disease	Izquierdo 2010	aOR 4.79 (2.03-11.32)	<0.001
	nil	Marrie 2004	reference	
	1 co-morbid disease		aOR 1.5 (1.23-1.83)	<0.05
	2 co-morbid diseases		aOR 2.07 (1.59-2.68)	<0.05
	3 or more co-morbid diseases		aOR 2.05 (1.45-2.89)	<0.05
	AIDS	Tang 2014	aOR 1.99 (1.06-3.74)	0.03
	CCF	Jasti 2008	aOR 1.6 (0.9-3.0)	non-significant
		Tang 2014	aOR 1.18 (1.07-1.29)	<0.01
		Zasowski 2014	RR 1.78 (0.9-3.52)	<0.25
	PVD	Micek 2014	OR 3.64 (2.27-5.84)	<0.01
	CAD	Jasti 2008	aOR 2.7 (1.5-4.7)	<0.05
	COPD	Jasti 2008	aOR 2.3 (1.3-4.1)	<0.05
		Zasowski 2014	RR 1.87 (0.93-3.68)	<0.25
	Asthma	Jasti 2008	aOR 2.0 (1.0-4.1)	non-significant

	LTOT	Jasti 2008	aOR 1.7 (0.7-4.0)	non-significant
	ILD	Jasti 2008	aOR 1.2 (0.4-4.1)	non-significant
	Diabetes Mellitus	Jasti 2008	aOR 1.4 (0.7-2.5)	non-significant
		Zasowski 2014	RR 1.01 (0.49-2.06)	non-significant
	Peptic Ulcer Disease	Tang 2014	aOR 1.24 (1.02-1.5)	0.03
	CKD	Tang 2014	aOR 1.18 (1.06-1.33)	<0.01
		Zasowski 2014	RR 1.05 (0.49-2.24)	non-significant
	Malignancy	Tang 2014	aOR 1.17 (1.06-1.28)	<0.01
		Zasowski 2014	RR 0.76 (0.28-2.21)	non-significant
	Alcoholism	Zasowski 2014	RR 4.04 (1.78-9.15)	<0.25
	HIV	Zasowski 2014	RR 0.57 (0.08-3.86)	non-significant
	CVA	Zasowski 2014	RR 0.29 (0.04-2.03)	non-significant

b) Admission risk factors

Risk Factor	Study	Outcome measure	p value
CURB65 >=1	Brettel 2011	OR 2.00 (0.55-7.28)	
Increasing CURB65 score	Micek 2014	OR 1.46 (1.27-1.68)	0.007
PSI >90	Adamuz 2011	OR 0.65 (0.32-1.31)	0.22
PSI class I	Jasti 2008	reference	
PSI class II		OR 0.7 (0.2-2.9)	non-significant
PSI class III		OR 0.8 (0.2-3.21)	non-significant
PSI class III	Zasowski 2014	RR 1.43 (0.73-2.83)	non-significant
PSI class IV	Jasti 2008	OR 0.8 (0.2-3.0)	non-significant
PSI class IV	Zasowski 2014	RR 0.7 (0.35-1.38)	non-significant
PSI class V	Jasti 2008	OR 1.3 (0.3-5.3)	non-significant
Length of stay (per day)	Brettel 2011	OR 1.01 (0.98-1.03)	non-significant
Haemophilus influenzae B CAP	Adamuz 2011	OR 1.7 (0.59-4.88)	0.32
Antibiotics <4hours admission	Houck 2004	OR 0.95 (0.85-1.06)	0.34
Guideline concordant treatment duration	Madaras-Kelly 2016	OR 1.1 (0.8-1.7)	0.58
Tazocin	Brettel 2011	OR 2.50 (0.80-7.78)	not reported
Few CAP versus many CAP cases€	Klausen 2012	HR 0.84 (0.7-1.0)	non-significant
Small hospital versus large hospital		HR 0.75 (0.67-0.84)	<0.01
>50 CAP cases versus < 50 CAP cases	Marie 2004	HR 1.02 (0.8-1.3)	non-significant

€ no objective criteria for few or many CAP cases defined

c) Discharge risk factors

Risk Factor	Study	Outcome measure	p value
Stability at discharge	Adamuz 2011	OR 1.8 (0.41-7.93)	0.44
Any instability at discharge	Micek 2014	aOR 1.5 (0.8-2.7)	
1 instability	Adamuz 2011	aOR 1.3 (0.7-2.5)	
2 or more instabilities		aOR 3.5 (1.0-12.4)	0.02

5.4 Discussion

This systematic review is the first to estimate pooled 30-day readmission rate in a broad but well-defined population of hospitalised adult patients with radiographically confirmed CAP. Thirty-day readmission rate was estimated to be 10% across all included studies. Variation in 30-day readmission was observed by geographic location; 12% in North America, 8% in Europe, and 8% in studies from 'other' locations. Estimates of 30-day readmission rate were significantly higher in large database and retrospective studies. Readmissions within 30-days were predominantly pneumonia unrelated, with cardiovascular events accounting for 20%. Co-morbid disease, socio-economic status, and clinical instability at point of discharge were identified as risk factors associated with 30-day readmission at qualitative summation of the limited available data.

5.4.1 Results in context

The results of this review are consistent with previous studies investigating readmission rates and risk prediction models; Firstly, a systematic review of risk prediction models for readmission concluded that factors assessed by studies varied substantially, infrequently included biomarkers or vital signs (especially stability on discharge), and that such models had modest predictive ability for readmission.[131] Secondly, in their cohort study of readmissions post-CAP, Millet et al concluded that whilst co-morbidities and frailty factors contributed to risk of readmission, changes in service provision and patient behaviour were more important, and that these are rarely captured in research studies or service quality metrics.[199] This is likely to be one explanation for variable readmission rates within and across conditions.

This review demonstrated that 30-day readmission rate was significantly higher in North America compared with Europe and Other countries. Possible explanations for this observation include differences in socio-economic status, access to public healthcare, and healthcare system organisational arrangements by location. The impact of geographical location on readmission rate has been reported previously in other acute medical conditions including acute myocardial infarction, asthma, chronic obstructive pulmonary disease, congestive cardiac failure, stroke, diabetes, and total hip replacement. [133,200] It is worth noting that when taken together these studies do not demonstrate a consistent impact on readmission rate across different acute conditions when comparing geography alone. Possible explanations for this observation might include condition-specific differences, the multifactorial nature of readmission, regional / geographical expertise with individual conditions, or other as yet unexplored reasons.

Previous studies have reported risk factors for readmission following an episode of CAP. Similar to this review, co-morbid illness is the most significant pre-admission risk factor.[145,166,167,170,178,185,189,196] One explanation for this association may be reverse causation whereby patients with co-morbid illnesses are at an increased likelihood of being admitted to hospital and are also concurrently more susceptible to acquiring CAP as a complication of their underlying illmess.[201]Alternatively, patients with comorbid illnesses are more at risk of developing complications following pneumonia, and that some of these complications emerge during the 30-day period following discharge. [202,203]

Apart from the study by Mieck *et al*, no study identified factors assessed at the time of hospital admission which were strongly associated with readmission. This lack of association is consistent with clinical experience; following adequate treatment, admission factors would not be expected to influence subsequent readmission. Instead, clinical stability at the time of hospital discharge should be more relevant, as reported in the influential study by Halm *et al* conducted in the US, [55] which demonstrated that clinical instability at discharge was a predictor of readmission.

Finally, this study adds further evidence to the previously reported association between cardiovascular events and CAP, [202,204,205] with cardiovascular-related readmissions accounting for 1/5th of all 30-day readmissions. One possible explanation for this observation is that both CAP and coronary artery disease share common risk factors for their development, including but not limited to, increasing age, presence of co-morbid disease, and lifestyle factors such as smoking.[203] Indeed, the greatest risk factor for CVEs in CAP is pre-existing coronary artery disease.[202]

5.4.2 Strengths and limitations

This is the largest systematic review of 30-day readmission in a well-defined population of patients discharged following hospitalisation with CAP, including 148,285 individual patients from 11 countries.

The review was conducted in accordance with PRISMA statement. Eligibility criteria were rigorously applied to exclude studies which included cases of hospital-acquired, aspiration pneumonia, and post-obstructive pneumonia due

to lung cancer. It is accepted that these patients represent distinct pneumonia cohorts with different clinical and pathophysiological characteristics, likely to influence 30-day readmission rate and risk. Previous evidence indicates that in retrospective database studies up to 40% of WHO-ICD coded cases of pneumonia were in fact cases of HAP.[206] It follows that in studies which do not adequately define CAP, or exclude cases of HAP, reported 30-day readmission rates are likely to diverge from studies including only true, radiographically confirmed CAP.

This review reports high levels of heterogeneity across the pooled estimates, as demonstrated by the I^2 statistic. These were not substantially reduced by any of the pre-specified subgroup analyses indicating that 30-day readmission rate is unlikely to be dependent on a single variable but rather a complex interplay of multiple factors across varying domains. It is likely that patient-specific, wider social, healthcare system, political and international factors are involved. Indeed, several authors have suggested that hospital readmission rate is multifactorial.[135-139,207,208]

The included studies did not provide sufficient detail to allow further categorisation of a pneumonia-related readmission. We have previously demonstrated that approximately 70% of patients' re-consult healthcare providers within 28-days of discharge following an episode of CAP, frequently with persistent symptoms as part of normal recovery as opposed to an acute deterioration or untreated infection.

5.4.3 Implications

It has been demonstrated that 30-day readmission rate following an episode of CAP varies substantially, with the presence of comorbid disease conferring the greatest risk of readmission. Large database studies were demonstrated to over-estimate readmission rates (13% in database studies, 9% in non-database studies). One explanation for this could be incomplete case definition, which in turn could misrepresent healthcare provider performance, with subsequent financial and governance implications at an institutional level.

Cardiovascular events are responsible for 1/5th of all readmissions at 30-days, whilst pre-existing evidence suggests that the risk of CVEs persist for years following an episode of CAP. As such, the potential burden of cardiovascular disease for both patients and healthcare providers following an episode of CAP is substantial. Future research should focus on; a) the development of a core data set for studies examining 30-day readmission following CAP, b) development of risk prediction models which include co-morbidity, functional and socioeconomic status, and stability at discharge, and c) development and application of risk prediction models to identify patients at risk of CVEs following an episode of CAP. Additional evidence is needed to inform the implementation of interventions targeted at preventing the development of CVEs in these patients.

5.4.4 Conclusion

Thirty-day readmission following hospitalisation for an episode of CAP was estimated to be 10% across included studies. Substantial heterogeneity was demonstrated which could not be accounted for by any of the subgroup analyses. Further work to define a more representative measure of in-hospital

quality of care is needed, along with predictors of risk of readmission, and interventions to reduce cardiovascular morbidity in recovery.

Chapter 6: Assessing recovery following an episode of Community-Acquired Pneumonia – an exploratory study

6.1 Introduction

As outlined in chapter 1, community-acquired pneumonia is a leading infective cause of hospital admission,[6] with the majority of patients surviving their inpatient stay to be discharged into the community to continue their recovery. As previously highlighted, there is marked disparity between physician-rated clinic cure, radiographic resolution, and patient-reported symptom resolution and return to usual daily activity.[45-47,86,87]

Despite the demonstrable symptomatic and functional burden of disease experienced by patients during recovery there remains a lack of appropriate research in this area, including a poor understanding of;

a) The relationship between patient-reported symptoms and biological, physiological, or cognitive markers of pathology,

b) The mechanisms that underlie recovery from pneumonia

c) The possible interventions that may improve recovery from pneumonia, including reducing patient morbidity and unplanned healthcare reconsultations.

The purpose of this exploratory study was to a) describe in a systematic manner the recovery process in adult patients discharged from hospital following an episode of CAP using well-validated assessment tools across clinically important domains, and b) to subsequently identify which of the employed tools to measure recovery are the most appropriate, acceptable, and tolerable for use in future studies of CAP recovery, and at what time points in follow-up.

6.2 Methods

6.2.1 Patient and public involvement

The protocol was conceived and designed in conjunction with the Nottingham Pneumonia Patient and Public Involvement Group (PPI), including recruitment of a nominated PPI co-applicant. The PPI group provided critical review of the study proposal and design, informing subsequent iterations of the protocol. The PPI co-applicant was involved in study management throughout, receiving frequent updates regarding participant recruitment, study conduct, and study amendments. The PPI group contributed to critical review of study result, and informed plans for their future dissemination.

6.2.2 Study Design

A prospective exploratory observational cohort study was conducted at 2 large teaching hospitals in UK between May 2018 and February 2020. Eligible patients were aged >16 years, including immunocompromised and HIV positive patients, with a clinical diagnosis of CAP. Community-acquired pneumonia was defined as; at least one lower respiratory tract symptom (breathlessness, new productive cough, pleuritic chest pain, fever), and an admission chest radiograph consistent with infection, and treated as for CAP by attending medical team. Patients were excluded from study recruitment if they; had been an inpatient within preceding 10 days, had a diagnosis of post-obstructive pneumonia secondary to lung cancer, active Tuberculosis, pneumonia likely secondary to aspiration, or evidence of cognitive impairment or language barrier such as to impair the ability to provide informed consent or participate in follow-up as per protocol,

including telephone consultation, or contraindications to performing lung function testing.

The study received ethical approval from the West Midlands - Solihull Research Ethics Committee (REC number: 18/WM/0117) (Appendix 3).

6.2.3 Patient population

Eligible patients admitted to hospital with CAP were identified and screened against study inclusion and exclusion criteria. Screening was undertaken during periods when clinic space and research staff availability would permit participant enrolment and adequate assessment during study follow-up. Convenience sampling was employed to facilitate recruitment of 20 CAP cases encompassing a range of participant age and pneumonia severity. All participants provided informed consent, which was reconfirmed at each subsequent study interaction. Patients received usual medical care at the discretion of the responsible medical team. A standardised proforma was employed to collect patient demographic and clinical characteristic data. All collected data was checked for accuracy, discrepancies reviewed and rectified, and then transferred to an electronic data management system (REDCAP Cloud, © 2015-2020, nPhase, Inc.).

Several domains were identified for assessment following a comprehensive literature review and subsequent discussion with PPI group members. These domains included functional capacity, symptomatology, cognition, and re-consultation, in addition to biological and radiographic markers of infection. Details of the assessments employed, and timing of measurement are outlined in table 6.1.

Table 6-1 Timing and details of patient assessments in CAP recovery study

Procedures	Visits							
	Enrolment	Discharge (Day 0)	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42
Informed Consent	X							
Baseline Clinical data	X							
Physiological Observations	X		X	X				X
CAP Symptom score		X*	X	X	X	X	X	X
Fatigue Questionnaires		X*	X	X	X	X	X	X
MRC Breathlessness		X*	X	X	X	X	X	X
Healthcare Utilisation Questionnaire			X	X	X	X	X	X
Biomarkers		X						
Urine sampling		X		X				X
Lung Function		X		X				X
MoCA		X						X
6MWD		X	X	X				X
TUG		X	X	X				X
Chest X-ray	X							X

MoCA; Montreal Cognitive Assessment, 6MWD; Six-minute walk distance. TUG: Timed up and go

** At discharge assessment a retrospective assessment (recalling their self-reported status / symptoms 6 weeks prior to acute illness) was completed by participants for CAP symptom score, Fatigue Questionnaires, and MRC breathlessness score.*

6.2.4 Outcome measures

The primary outcomes of interest were chosen to describe the trajectory of recovery in patients following an episode of CAP requiring hospitalisation and included;

a) Prevalence of CAP symptoms during follow-up, assessed using the CAP symptom score questionnaire, measured at discharge and weekly thereafter. The discharge assessment includes a retrospective, self-reported CAP symptom score 6-weeks prior to onset of acute illness.
b) Change in fatigue during follow-up, assessed using two different self-reported questionnaires, measured at discharge and weekly thereafter. The discharge assessment includes retrospective, self-reported fatigue questionnaires 6-weeks prior to onset of acute illness.
c) Change in cognitive status, as measured by the Montreal Cognitive Assessment (MoCA), assessed at discharge and 42-day follow-up
d) Change in functional capacity as assessed by comparing timed up and go and six-minute walk distance at discharge, 7-, 14-, and 42 days follow-up.
e) Change in spirometry as assessed by comparing forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), maximum inspiratory mouth pressure (MIP), and maximum expiratory mouth pressure (MEP) at discharge, 7-, 14-, and 42 days follow-up.

The secondary outcomes of interest were;

a) Proportion of participants completing each individual assessment at each time point, as a marker of tolerability and acceptability

b) Frequency of patient reported healthcare utilisation within 7 days, between 7 and 14 days, between 14 and 28 days, and after 28 days of follow-up,

6.2.5 Tools employed to assess outcome measures

6.2.5.1 CAP Symptom Questionnaire

The CAP-symptom questionnaire (CAP-sym) is a psychometrically validated, 18-item patient-reported tool to evaluate how bothersome CAP-related symptoms are using a 6-point Likert scale, [209] with higher scores representing more bothersome CAP-related symptoms. The CAP-sym has been used as an outcome measure in randomised controlled trials and observational studies of CAP, demonstrating responsiveness to treatment and consistency in scoring.[94,210] Within these studies the CAP-sym has been used to record the point prevalence, average score, and longitudinal change of symptoms at each follow-up assessment. It has also been used to model time to symptom recovery in a cohort of patients with CAP.[64]

6.2.5.2 Fatigue Assessment Scale

The Fatigue Assessment Scale is a 10-item scale used to evaluate symptoms of fatigue and has been used in patients with sarcoidosis and idiopathic pulmonary fibrosis to identify changes in patient-reported fatigue at up to weekly intervals.[211-215] Each item of the FAS is answered using a five-point, Likert-type scale ranging from 1 (“never”) to 5 (“always”). Items 4 and 10 are reverse scored. Total scores can range from 10, indicating the lowest level of fatigue, to 50, denoting the highest. A reduction in score across follow-up indicates a reduction in fatigue.

6.2.5.3 Modified Fatigue Impact Scale

The Modified Fatigue Impact Scale (MFIS) is a 21-item patient-reported scale designed to measure fatigue across three subscales (physical subscale, cognitive

subscale, psychosocial subscale, and total fatigue scale.) It is a shortened version of the original Fatigue Impact score[216] and has predominantly been employed to assess fatigue in patients with Multiple Sclerosis and Traumatic Brain Injury.[217,218] The MFIS has the advantage of being freely available and easy to administer whilst maintaining validity in these patients, [219] but thus far has not been employed to assess fatigue outside of these conditions. Higher total scores correspond with the presence of a greater degree of fatigue; hence reduction in MFIS score across follow-up indicates reduction in fatigue. The MFIS has been used to assess fatigue in patients with different respiratory conditions, including COPD, pulmonary fibrosis, and lung cancer.

6.2.5.4 Montreal Cognitive Assessment (MoCA)

The MoCA is a rapid screening test comprised of 30 questions to assess multiple domains of cognitive function including attention and concentration, executive function, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. A score of 27 or more corresponds with normal cognitive function. The MoCA has been deemed superior in detecting mild cognitive impairment when compared to alternative forms of cognitive assessment in patients with chronic lung disease and experiencing acute infective exacerbations.[220-223]

6.2.5.5 Timed up and Go

The timed up and go (TUG) test is an assessment of functional mobility initially developed for the assessment of mobility and balance defects in elderly adults. It requires the participant to rise from a chair, walk 3 metres as quickly and safely as able, turn around and then walk back to return to sitting. The TUG has

demonstrated high inter-rater and intra-rater reliability but has predominantly been used as a screening tool to identify elderly individuals who need a more detailed mobility assessment.[224-228]

6.2.5.6 Six Minute Walk Distance

The six-minute walk distance (6MWD) assesses the submaximal level of functional capacity by measuring the distance an individual can walk along a 30m corridor, at a pace determined by the participant, within 6 minutes. The 6MWD evaluates the global response of all organs and systems involved in exercise. It does not provide specific information about the function of each individual organ involved. It has been demonstrated to correspond to the functional exercise level of each individual for their activities of daily living, and therefore provides a representation of their daily functional capacity.[229-234]

6.2.5.7 Spirometry

Standard simple spirometry was employed for assessment of lung function in all participants, including forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC), assessed using a hand-held spirometer (Vitalograph Alpha Spirometer) by trained researchers. In addition, maximal inspiratory mouth pressures (MIPs) and maximal expiratory mouth pressures (MEPs) were also assessed as these been demonstrated to correspond with respiratory muscle function.

6.2.6 Statistical considerations

This exploratory study was not powered sufficiently to undertake in depth statistical analysis. The observed trends are presented using the appropriate

descriptive statistical methods depending on distribution of data, either; mean with 95% confidence intervals, or median with interquartile ranges. Change in pulmonary function was determined by comparing discharge pulmonary function test results with pulmonary function tests results at final follow-up. Unless participants are lost to follow-up or are unable or decline to complete pulmonary function testing, this was at 42-days follow-up assessment. Statistical analyses were conducted using Stata/IC 15 (©StataCorp. 2017).

6.3 Results

6.3.1 Study population

Of the 46 patients approached between July 2018 and December 2019, 20 agreed to participate in the study and were enrolled. However, one participant withdrew consent after enrolment but prior to assessments being completed (Figure 6.1). Participant baseline characteristics are presented in table 6.2. Eleven (57.9%) participants were female and average participant age was 58.5 years (range 29 – 79 years). Patient reported their World Health Organisation (WHO) performance status 6-weeks prior to onset of acute illness as 0 (asymptomatic and fully independent) in 18 out of 19 participants, whilst one participant reported their WHO performance status as 1 (symptomatic but completely ambulatory.) All participants reported deterioration in their WHO performance status at the time of discharge from hospital (table 6.2). Nine participants were never smokers, eight were ex-smokers, and two were current smokers. One or more co-morbid illnesses were present in 10 participants prior to their episode of CAP.

Figure 6-1: CAP recovery study flow diagram

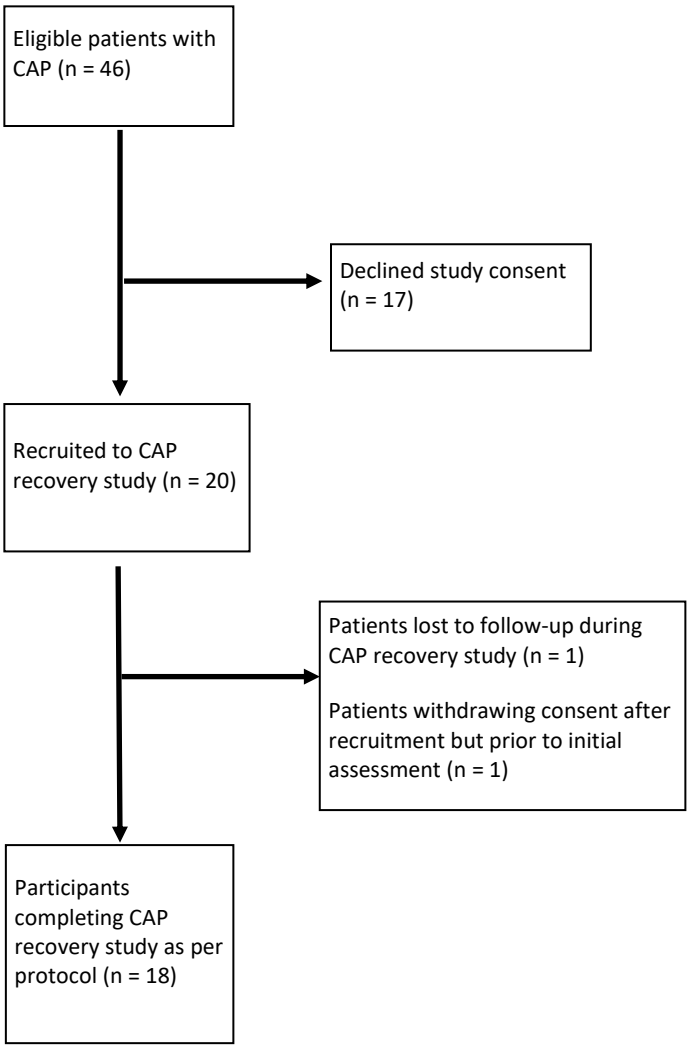


Table 6-2 Characteristics of CAP recovery study participants, n=19

Gender, male (%)	**8 (42.1)**	
Co-morbid disease prior to episode of CAP, n (%)		
0	9 (47.4)	
1	5(26.3)	
≥2	5(26.3)	
Chronic Lung Disease n (%)	6 (31.6)	
Cardiac Disease n (%)	3 (15.8)	
Musculoskeletal Disease n (%)	3 (15.8)	
Neurological Disease n (%)	2 (10.5)	
Chronic Kidney Disease n (%)	1 (5.3)	
Malignancy n (%)	1 (5.3)	
Gastrointestinal Disease n (%)	1 (5.3)	
Smoking status, n (%)		
Never Smoker	9 (47.4)	
Ex-Smoker	8 (42.1)	
Current Smoker	2 (10.5)	
Performance status, n (%)	6-weeks prior to admission	At discharge
0	18 (94.7)	0
1	1 (5.3)	15 (79.0)
2	0	1 (5.2)
3	0	3 (15.8)
4	0	0

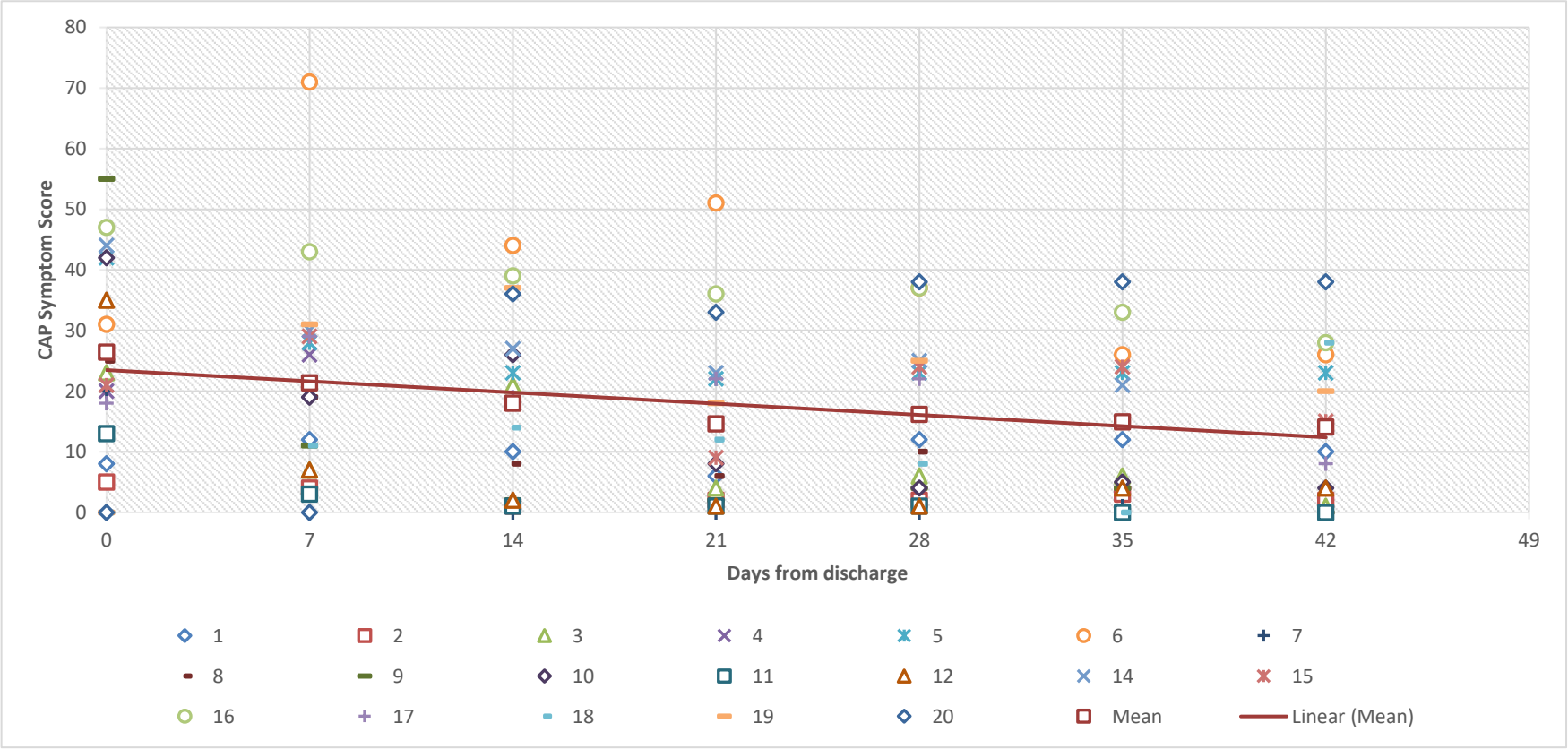
6.3.2 Primary Outcomes

6.3.2.1 Symptomatic recovery

Mean retrospective CAP symptom score, recalled by participants 6 weeks prior to acute illness, was 11 (95% confidence interval 4.8-17.8). Mean CAP symptom score at discharge and 42 day follow up were 26 (95% CI 19.9-32.9) and 14 (95% CI 8.8-19.3) respectively. The trends in CAP symptom scores for each participant are presented in figure 6.2.

Assessment of fatigue was performed using the two fatigue questionnaires with contrasting tolerability and results. The Fatigue Assessment Score (FAS) was reported to be challenging to complete by participants, with a mean FAS score at discharge of 25 (95% CI 21.7-28.4) which decreased at 42-days to 21 (95% CI 18.8-23.2). Similarly, the mean Modified Fatigue Impact Scale decreased across follow-up, from 39 (95% CI 31.3-47.6) at discharge to 18 (95% CI 10.1-25.9) at 42-days. However, the MFIS was reported as being easier to understand, complete, and described as more acceptable by participants.

Figure 6-2; Trends in CAP symptom score for individual participants in CAP recovery study



**No participant 13 as lost to follow-up, N=19*

6.3.2.2 Cognition

Seventeen participants completed MoCA tests at both discharge and 42-day follow up; the median MoCA score at discharge was 27 (range 21-30) and at 42-day follow-up was also 27 (range 22-30). At discharge, five participants had a score of less than 27 indicating cognitive impairment; three individuals demonstrated improvement in their MoCA scores to 27 or over (classified as normal), whilst the MoCA scores for the remaining two participants did not change and continued to signify significant cognitive impairment.

Comparing discharge and follow-up assessment; 5 (29.4%) participants had no change in their MoCA score, 6 (35.3%) participants demonstrated improvement, and 6 (35.3%) participants demonstrated a decline in their MoCA scores, 2 of whom declined sufficiently to have a significant cognitive deficit with a MoCA score less than 27.

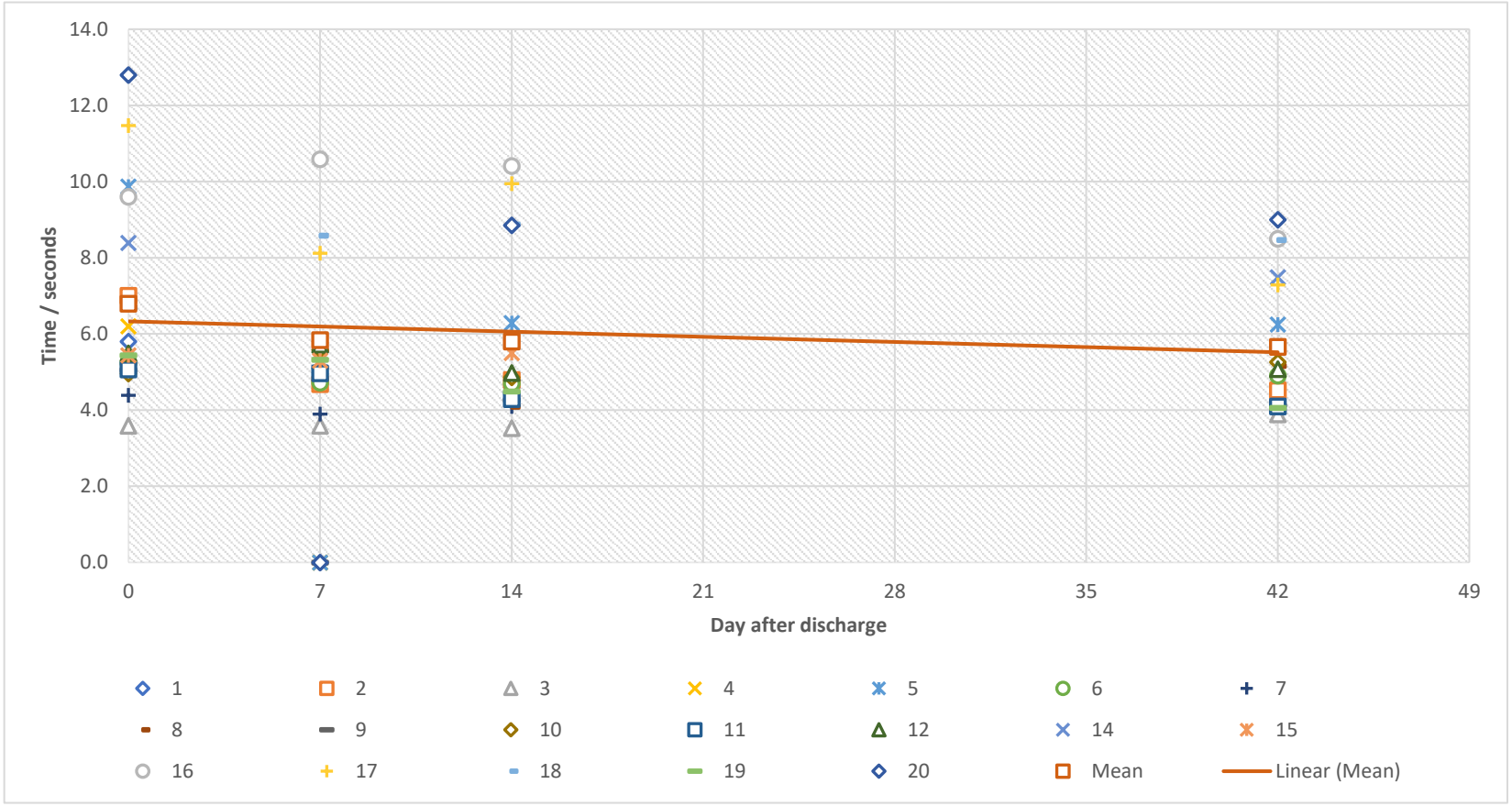
6.3.2.3 Functional recovery

The TUG and 6MWD trends for each individual participant are presented in figure 6.3 and 6.4. One participant was lost to follow-up and did not have a 42-day follow-up assessment. The mean TUG test results, along with standard deviations, for the remaining 18 participants at discharge, 7-, 14-, and 42-day follow-up were 6.8 seconds (±2.5), 5.8 seconds (±1.9), 5.8 seconds (±2.2), and 5.7 seconds (±1.7) respectively. Comparing difference between means at discharge and 42-day follow-up there was an average 1.1 second improvement. All participants had TUG results within the normal range defined by previous studies, although these studies were not in patients with CAP. Fourteen (77.8%) of participants improved their TUG result over the period of follow-up. Of the

four participants who saw a decline in their TUG results between discharge and 42-day follow-up, three had difference in their time of 0.5 second or less, whilst the fourth participant was 1.8 seconds slower at 42-day follow-up.

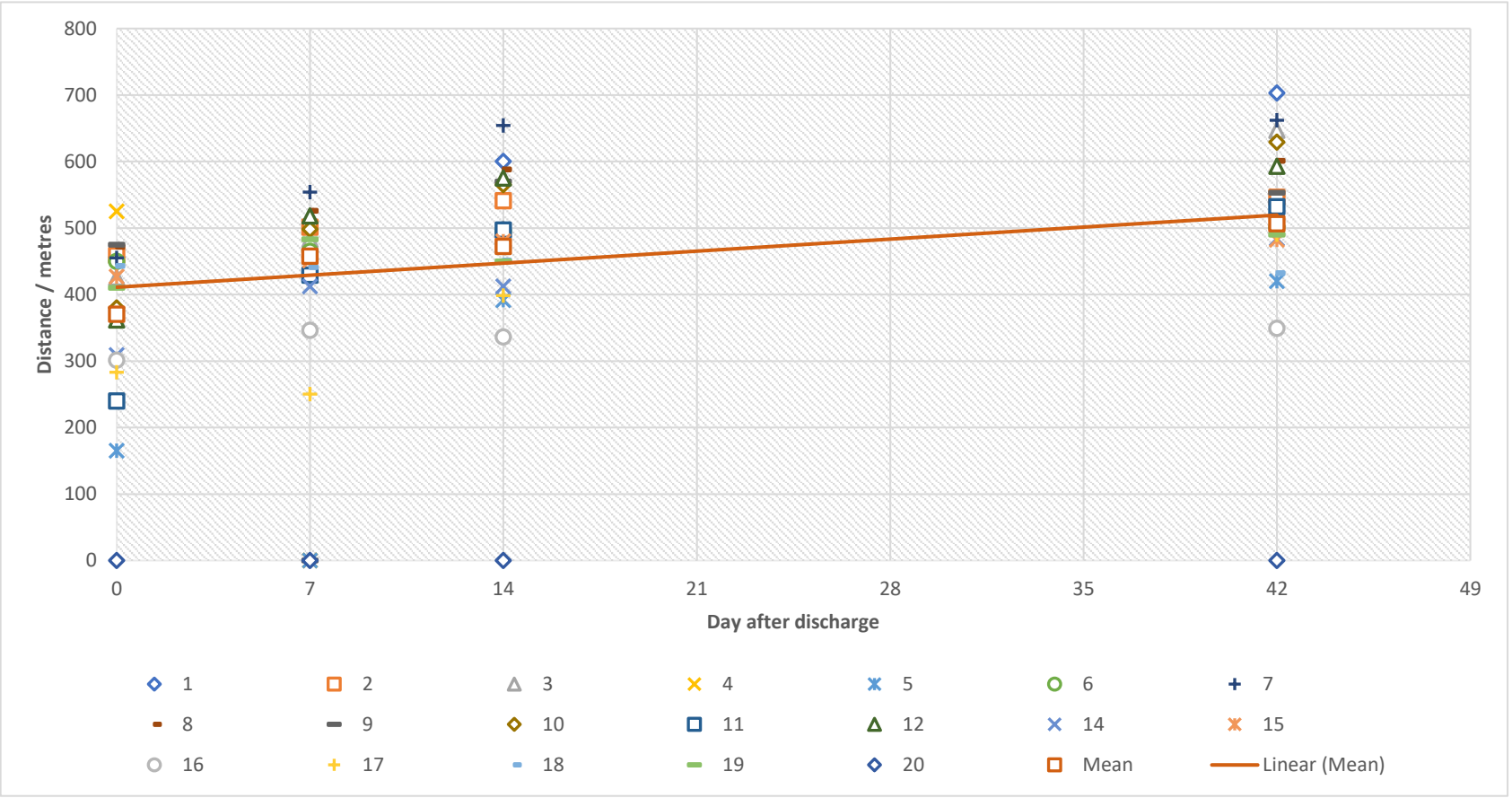
One participant was lost to follow-up, only recording a 6MWD at discharge. The mean six-minute walk test results for the remaining 18 participants, along with associated standard deviations at discharge, 7-, 14-, and 42-day follow-up were 370 metres (±129.0), 458 metres (±77.4), 472 metres (±144.7), and 506 metres (±156.1) respectively, with an average improvement between discharge assessment and 42-day follow-up of 136 metres. One participant recorded a 6MWD at each assessment of 0 metres, as they declined to attempt to walk and spent the duration of the assessment seated at the start line. Sixteen (84.2%) participants demonstrated an improvement in their 6MWD comparing discharge assessment to 42-day follow-up, with eight (42.1%) increasing their distance walked by over 200metres. Of the two participants who did not improve their distances, one participant did not attempt the 6MWD as outlined above, whilst the other had an 11-metre reduction in their distance when comparing discharge assessment and 42-day assessment.

Figure 6-3: Trends in timed up and go for individual participants in CAP recovery study



**No participant 13 as lost to follow-up, N=19*

Figure 6-4: Trends in six-minute walk distance for individual participants in CAP recovery study



**No participant 13 as lost to follow-up, N=19*

6.3.2.4 Pulmonary function

On average, there was an improvement across all the measured pulmonary function tests between discharge and final measurement, with final measurement predominantly obtained at 42-day follow-up appointment (one participant only completed discharge pulmonary function testing, whilst two participants' final measurements were recorded at 14-day follow-up and did not complete measurement at 42-days). Individual trends in pulmonary function tests are presented in Table 6.3 and 6.4.

All participants improved their FEV1 across study follow-up, with a mean difference in FEV1 of 570mls (±360mls) when comparing discharge to final recorded measurement. Similarly, 94% of participants demonstrated improvement in their FVC, with a mean difference in FVC of 570mls (±470mls). Peak expiratory flow rate measurements were more variable across the study cohort, but the difference in means between discharge and final assessment demonstrated an average improvement of 12.1 litres/min (±180.9 litres/min).

Maximal inspiratory and expiratory mouth pressure measurements were recorded in only 12 (63%) of participants due to the limited availability of appropriately trained researchers to conduct these assessments. The mean difference between discharge and final follow-up measurement were 32 cmH20 (±39.1) increase in MIP, and 0 cmH20 (±20.0) change in MEP.

Table 6-3; Trends in FEV1, FVC, and PEFR across CAP recovery study follow-up

	FEV1 (litres)			FVC (litres)			PEFR (litres/min)		
	Discharge	End of study*	Difference	Discharge	End of study*	Difference	Discharge	End of study*	Difference
1	3.32	3.81	0.49	4.2	5.56	1.36	504	608	104
2	2.48	2.61	0.13	3.29	3.3	0.01	382	428	46
3	2.24	2.79	0.55	2.89	3.53	0.64	414	510	96
4	1.69	-	-	2.58	-	-	324	-	-
5	0.98	1.07	0.09	1.34	1.62	0.28	273	288	15
6	1.75	2.07	0.32	2.86	2.81	-0.05	265.8	287.4	21.6
7	3.31	4.29	0.98	4.08	4.93	0.85	393.6	652.8	259.2
8	2.66	3.47	0.81	4.13	4.35	0.22	378	457.2	79.2
9	3.31	4.45	1.14	4.13	4.88	0.75	681	487.2	-193.8
10	1.46	2.77	1.31	1.78	3.36	1.58	285.6	531.6	246
11	1.24	2.11	0.87	1.53	2.56	1.03	325.8	436.8	111
12	2.61	2.8	0.19	3.28	3.46	0.18	425.4	430	4.6
14	4.36	5.15	0.79	4.85	5.9	1.05	446	593	147
15	1.9	2.48	0.58	2.76	3.3	0.54	462	250	-212
16	2.18	2.84	0.66	2.74	3.49	0.75	731	449	-282
17	1.01	1.32	0.31	2.03	2.22	0.19	258	181	-77
18	1.29	1.6	0.31	1.86	2.26	0.4	166	378	212
19	2.27	3.25	0.98	3.12	4.02	0.9	475	520	45
20	2.23	2.57	0.34	3.18	3.32	0.14	647	255	-392
Difference between means			0.57(±0.36)			0.57(±0.47)			12.1 (±180.9)

** End of study spirometry result refers to the last recorded measurement during follow-up, and could be at 7-, 14, or 42-day hospital follow-up assessment.*

Table 6-4; Trends in MIP and MEP across CAP recovery study follow-up

	MIP (cm/H_20)			MEP (cm/H_20)		
	First Test	Last Test	Difference	First Test	Last Test	Difference
1	93	102	9	112	141	29
2	81	78	-3	61	59	-2
3	65	91	26	69	65	-4
4	49	-	-	110	-	-
5	18	55	37	53	69	16
6	76	84	8	96	108	12
7	101	89	-12	101	101	0
8	51	89	38	69	57	-12
9	51	84	33	51	64	13
10	60	198	138	157	161	4
11	54	81	27	63	50	-13
12	65	104	39	76	118	42
14	86	153	67	93	60	-33
15	-	-	-	-	-	-
16	77	-	-	117	-	-
17	-	-	-	-	-	-
18	-	-	-	-	-	-
19	108	-	-	97	-	-
20	-	-	-	-	-	-
Mean difference			32(±39.1)			0(±20.0)

6.3.3 Secondary Outcomes

6.3.3.1 Assessment of tolerability

The number and proportion of participants completing each of the specified assessments during follow-up are presented in tables 6.5 and 6.6. Three participants declined to attend hospital for their 7-day follow-up as they did not feel physically able to travel but all three completed a telephone consultation in lieu. Another three participants did not have completed questionnaires from discharge available for analysis; two questionnaires were not fully completed by participants due to impaired cognition / impaired concentration, whilst the questionnaire for a third patient was not completed correctly and therefore was not included. For the remaining 16 participants, questionnaires to assess symptoms and fatigue were completed consistently throughout follow-up, achieving between 84.2% and 94.7% completion rates.

In general, assessments of functional capacity such as pulmonary function and exercise testing were less likely to be tolerated by participants at their 7-day follow-up appointment; proportion of participants attempting the 6MWD and TUG at discharge, 7-, 14-, and 42-days were 100%, 78.9%, 94.7% and 94.7% respectively.

Pulmonary function tests (FEV1, FVC, PEFR, MIP & MEP) were completed by 100% of participants at discharge, whilst 84.2% of participants completed FEV1, FVC, and PEFR measurement at 42-days, and 80.0% of those in who staff training permitted assessment completed MIP and MEP measurement at the same time point.

Table 6-5: Number and proportion of participants completing assessments measuring symptoms in CAP recovery.

Day	Fatigue Assessment Score	CAP Symptom Score	Multidimensional Fatigue Inventory
Retrospective*(n)	11	17	11
Discharge (n)	16	16	16
Day 7 (n)	18	18	17
Day 14 (n)	18	18	18
Day 21 (n)	18	18	18
Day 28 (n)	18	18	18
Day 35 (n)	16	16	16
Day 42 (n)	18	18	18

** Retrospective = 6 weeks prior to onset of acute illness as recalled by participants*

Table 6-6: Number and proportion of participants completing assessments measuring functional ability and lung function in CAP recovery.

Day	6MWD	TUG	FEV1	FVC	PEFR	MIP*	MEP*
Discharge (n)	19	19	19	19	19	15	15
%	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Day 7 (n)	15	15	15	15	15	10	10
%	78.9	78.9	78.9	78.9	78.9	66.7	66.7
Day 14 (n)	18	18	18	18	18	12	12
%	94.7	94.7	94.7	94.7	94.7	80.0	80.0
Day 42 (n)	18	18	16	16	16	12	12
%	94.7	94.7	84.2	84.2	84.2	80.0	80.0

6MWD = Six-minute walk distance, TUG = timed up and go test, FEV1 = Forced expiratory volume in 1 second, FVC = forced vital capacity, PEFR = Peak expiratory flow rate, MIP = maximal mouth inspiratory pressure, MEP = maximum mouth expiratory pressure

** Only 15 participants were able to participate in measurement of MIP and MEP due to staff training and competency in performing this assessment.*

6.3.3.2 Healthcare utilisation in recovery

Participants consulted healthcare services on 6 occasions during study follow-up. Two participants (10.5%) attended their GP practice within 7 days of discharge seeking further antibiotics, whilst 4 participants (21.1%) consulted with their GP for an extension to their sick note between 15 and 42days after discharge. There were no secondary care consultations and none of the study participants were readmitted to hospital within 90 days of discharge from hospital.

6.4 Discussion

This is the first prospective study to evaluate recovery following an episode of hospitalised CAP over multiple clinically important domains including symptoms, functional activity, exercise capacity, lung function, and cognition. Importantly, the study included an assessment of the tolerability and acceptability of each of the assessment tools employed to guide their use in future research.

Overall, participants demonstrated an improvement in their symptoms, functional ability, and physical capacity from discharge to follow-up at 42-days. The employed assessments demonstrated variable tolerability and acceptability to patients. Questionnaires demonstrated the highest levels of tolerability and acceptability, regardless of whether conducted in-person or remotely. In contrast, assessments of exercise capacity and lung function, requiring attendance at hospital, were less tolerable in the initial days following discharge, with increasing acceptability and tolerability with time from discharge.

6.4.1 Research in Context

This study demonstrates that persistent symptoms and functional impairment are common during recovery following CAP, consistent with the studies outlined in chapters 3 and 4and that of other authors.[44,52,64,87,114,118,235,236] Importantly, the symptoms and functional impairment experienced by patients in recovery following CAP are greater that those reported in the general population and similar to those reported by patients with several chronic diseases as outlined below.

Fatigue was assessed using two questionnaires, the FAS and MFIS, and persisted in over 50% of participants at 42-days, with a trend towards reducing severity as follow-up continued, similar to previous studies in CAP recovery,[13,52,64,87] and substantially higher than levels reported in the UK general population based on GP database studies..[237,238] The FAS was reported as being difficult to understand and complete by participants, whereas the MFIS was more acceptable to participants. Furthermore, levels of fatigue at 42-day follow-up following CAP are similar to those reported in patients with chronic lung diseases including COPD, pulmonary fibrosis, and sarcoidosis.[212,215,239-244] The pathophysiology of fatigue in CAP, reported by patients to be the most persistent and intrusive symptom, has not been established, nor has its relevance to other clinically important outcomes such as re-hospitalisation or mortality. However, in patients with COPD, persistent fatigue has been associated with increased risk of hospitalisations.[245] Additional research is needed to determine if a similar association between fatigue and development of complications is present in patients recovering from CAP. The MFIS should be used to assess fatigue, as it was most acceptable and tolerable to patients whilst continuing to demonstrate clinically relevant changes.

This study demonstrated that whilst there was no difference between average MoCA scores when comparing baseline assessment and 42-day follow-up, 1/3rd of participants demonstrated a decline in their MoCA score over this period, with two sufficiently impaired (MoCA score 26 or less) at 42-day follow-up that further specialist assessment in a dedicated memory service was warranted. A

study of cognition following an episode of CAP by Girard et al demonstrated that 1/3rd of all participants, and 20% of those less than 65 years old, had moderate-severe cognitive impairment at 2 and 12 month follow-up, [246] whilst another study by Davydow et al reported that patients were 2.6 times more likely to experience persistent cognitive impairment following hospitalisation for an episode of CAP compared to hospital admission for heart failure or stroke.[247] Furthermore, acute infective episodes have been demonstrated to be associated with cognitive impairment in patients with COPD[221-223]and in survivors of sepsis.[248-251] As this was an exploratory study, and not powered to determine statistical significance, future studies in CAP recovery should include an assessment of cognitive function at discharge and follow-up.

Exercise testing during follow-up demonstrated improved tolerability and acceptability in the latter phases of this study, especially from 14 days following discharge. The 6MWD, as a surrogate marker of submaximal exercise capacity and therefore daily activity, may prove to be significant in identifying patients who have not returned to their functional baseline and who might benefit from interventions aimed at improving this. The TUG results were universally within the normal range for this assessment, although these ranges were defined in studies outside of CAP, generally in elderly, frail adults as a screening tool for functional impairment requiring further assessment and rehabilitation. As such TUG test did not identify participants with functional impairment in our cohort. Further large observational studies of CAP recovery, powered to define normal recovery of exercise capacity as well as to detect statistically significant

impairment of exercise capacity are required and should use the 6MWD as an assessment tool in preference to the TUG.

Pulmonary function testing was broadly well tolerated and acceptable for study participants, with FEV1 and FVC demonstrating consistent improvement in all participants. Simple spirometry (FEV1 and FVC) is widely available across secondary care, with standardised protocols for measurement and familiarity to clinicians and researchers. Future studies of CAP recovery should continue to measure FEV1 and FVC to define normal recovery and correlate these physiological parameters with symptoms and functional capacity. Suggested timing of assessment includes at discharge and not before 42-days follow-up, with additional research required to determine if repeat measurement beyond this is appropriate.

Less than two thirds of participants underwent assessment using maximal inspiratory and expiratory mouth pressures, primarily due to researcher training / competence at performing this assessment. Despite our small sample size, these measurements demonstrated substantial variability with wide standard deviations and did not identify a consistent trend. Furthermore, other studies have demonstrated significant intra-observer and inter-observer variability with MIPs and MEPs, in addition to their lack of widespread frontline use, both of which limit their application in real-world settings.[252-255]

Since this study was conducted, the global SARS-COV-2 pandemic and associated conditions of COVID-19 disease and 'long-COVID' have generated unparalleled interest, and subsequently research studies, in patient recovery following an

acute infectious respiratory insult. Although CAP and COVID-19 are distinct disease process in terms of pathophysiology,[256,257] the impairments experienced during the recovery phase following both are remarkably similar; a) persistent symptoms including breathlessness, cough and fatigue, b) functional impairment including delayed return to usual daily activity and occupation, c) impaired exercise tolerance and pulmonary function, and d) cognitive impairment. Studies of COVID-19 have described that over 50% of participants report not to have recovered from their COVID-19 illness at 6- and 12- month follow-up,[258-261] whilst a meta-analysis of COVID-19 recovery described persistent fatigue in 32.5% of participants and breathlessness in 22% at 4months and beyond.[262]

As this study of recovery following an episode of CAP demonstrates a trajectory of recovery over the initial 6 weeks, but with persistence of symptoms and functional impairment in most participants at 42-days follow-up, it would be more appropriate to assess CAP patients later during their recovery journey, as has been done in COVID-19 recovery studies. This would reduce the initial burden on patients from assessments during the early part of their recovery whilst still permitting identification of those individuals with abnormal persistence of symptoms and functional impairment that may be amenable to interventions to reduce morbidity.

Furthermore, the studies in COVID-19 have recruited larger numbers of patients than those available for CAP recovery and have used different assessment tools to measure recovery across domains, such as FACIT for fatigue, PHQ9 for depression, GAD7 for anxiety, EQ5D-5L for functional activity, and the

incremental shuttle walk test. Given the large numbers of participants assessed with these tools in a similar acute respiratory infective disease, future studies of CAP recovery should utilise these tools and the evidence generated for their acceptability and tolerability.

6.4.2 Strengths and Limitations

This represents the first prospective study of recovery following an episode of community-acquired pneumonia and includes an attempt to define appropriate timing and assessment tools across a variety of domains. The study employed several assessment methods within each domain, conducted under real-world conditions, with the aim of determining which was most tolerable for patients and informative for clinicians. It is accepted that there are likely to be other domains outside of those investigated, such as nutritional status, sleep quality and duration, and psychosocial support structures, which are likely to be important factors in recovery.

Another limitation of this study was the absence of qualitative data collected from participants to provide feedback about their experience of being assessed during their recovery. Anecdotal evidence from participants highlighted that attending hospital within the initial 4 weeks following discharge was challenging and bothersome for some participants, whilst some participants expressed dissatisfaction with individual measurement tools employed. However, most participants continued to complete these assessments as planned, and therefore looking only at proportions of completed assessments at each visit does not adequately represent their experience. Furthermore, unintended consequences of study participation, including increased follow-up with access to support and advice from the study team was not captured. Furthermore, the sample size of this cohort, recruited from a single centre in the UK, was not adequately powered to adequately demonstrate trends in recovery, define normal recovery, or determine factors associated with impaired recovery.

6.4.3 Implications of research

A large, prospective, multi-centre, cohort study is required to define normal recovery following an episode of hospitalised CAP and to evaluate if pre-admission, admission, and/or discharge factors can accurately and reliably predict patients a risk of delayed / abnormal recovery. Assessments should be undertaken at time of discharge, including a retrospective assessment of symptoms and functional capacity, with subsequent assessments at 4-6 months and 10-12 months. This work should include a nested qualitative study to gather more detailed patient experience of the tolerability and acceptability of assessments during recovery.

6.4.4 Conclusions

Recovery following an episode of hospitalised CAP needs to be further characterisation in an adequately powered, prospective observational cohort study. This study provides valuable information about the appropriate assessments in CAP recovery, including their tolerability, acceptability, and timing. Patient reported outcome measures including symptom burden and functional activity can be adequately assessed using questionnaires either face-to-face or remotely throughout recovery, but assessments of function, including lung function and exercise testing should be avoided until at least 6 weeks following discharge.

Chapter 7: Inspiratory Muscle Training (IMT) for adults discharged from hospital with community-acquired pneumonia (CAP) – a feasibility study

7.1 Introduction

As outlined in chapter 1, patients experience a substantial burden of disease following hospitalisation for an episode of CAP. The physiological basis for this morbidity is poorly understood. One potential mechanism for slow recovery is abnormal respiratory muscle function in the post-pneumonia period.

Respiratory muscle strength has been implicated in the perception of breathlessness and fatigue in healthy volunteers. Mechanisms thought to be involved include afferent neural input from respiratory muscles, [263,264] exercise-induced peripheral muscle fatigue, [265,266] and neurally-mediated reflex reduction in blood flow.[267] Small scale studies of various physiological parameters in patients following an episode of CAP have demonstrated several different defects at diagnosis and in follow-up including restrictive spirometry, reduced skeletal muscle strength, and impaired exercise capacity.[268,269]

Several different methods can be employed to investigate respiratory muscle function, including; maximal inspiratory and expiratory pressures; magnetic stimulation of phrenic nerve accompanied by measurement of inspiratory mouth pressure, inspiratory oesophageal pressure, or inspiratory trans-diaphragmatic pressure; and ultrasound assessment of diaphragm.[270] The former is most readily available, easily administered, and tolerable for subjects, but requires patient understanding and co-operation. Pressure measurements are invasive, requiring placement of catheters nasally into distal oesophagus and stomach, and are not readily available in most centres due to local expertise / experience. Ultrasound

measurement in operator-dependent, with substantial inter-operator variation, and is also influenced by patient habitus.

Inspiratory muscle training (IMT) aims to increase respiratory muscle strength through regular resistance training predominantly directed at the inspiratory muscles. In healthy volunteers IMT increases the strength and endurance of the respiratory muscles by inducing structural and robust adaptations within both the obligatory and accessory musculature,[266,271] increasing diaphragm thickness,[272,273] and altering the composition of type I and type IIa muscle fibres.[274]

Inspiratory muscle training has demonstrated benefits in several different patient groups; reduced dyspnoea perception and discomfort in chronic obstructive pulmonary disease,[275,276] increased strength and endurance of respiratory muscles in patients after a cerebrovascular event,[277] increased lung volumes, respiratory muscle strength, and exercise capacity in elderly patients;[273] prevention of post-operative pulmonary complications in patients undergoing coronary artery bypass graft;[278] and reduced perception of breathlessness in patients with lung cancer and congestive cardiac failure.[279,280]

However, trials of IMT in patient groups have not all demonstrated benefit, frequently suffering from poor methodological quality and small sample size; a Cochrane review of IMT in patients with asthma and a systematic review of IMT in patients with cystic fibrosis both concluded that methodological variation and small samples size in the available studies limited accurate assessment of IMT.[281,282]

To date, IMT has not been examined in patients following an episode of CAP. Given the substantial symptoms and functional impairment experienced by patients in recovery, an intervention to reduce this burden is required. It is unknown if IMT is an acceptable intervention for this group of patients. This feasibility study aimed to determine the safety and tolerability of IMT following hospitalisation for CAP.

7.2 Methods

7.2.1 Patient and Public Involvement

The Nottingham Pneumonia Patient and Public Involvement (PPI) Group contributed to study design at all stages. Members of PPI group participated in initial assessment of device feasibility, frequency, and content of follow-up assessment, and reviewed the proposed training schedule and intensity. The training schedule was modified based on PPI group input, incorporating a two-week induction phase followed by a seven-week training phase, as outlined below. The study received ethical approval from Nottingham Research Ethics Committee (REC number: 17/EE/0043) (Appendix 3).

7.2.2 Study design

A prospective observational cohort study was conducted of adult patients (>16 years) admitted to a participating hospital between February 2017 and April 2018 with a clinical diagnosis of CAP. Community-acquired pneumonia was defined as: the presence of one or more symptom of acute lower respiratory tract infection (cough, increasing breathlessness, sputum production, chest pain, and fever); evidence of acute infiltrates consistent with a respiratory infection on admission plain chest radiograph; and treated by the clinical team for CAP. Exclusion criteria included; inability to understand verbal or written information in English, hospital admission within preceding 10 days, active tuberculosis, post-obstructive pneumonia secondary to lung cancer, aspiration pneumonia, World Health Organisation performance status 2 or greater prior to admission, inability to provide informed consent, unlikely or unable to comply with telephone follow-up post-discharge, inability to perform required interventions during

follow-up, or presence of a contraindication to pulmonary function testing. Convenience sampling was conducted from identified eligible patients. Following informed consent, patient demographics and clinical characteristics were collected using a standardised proforma.

7.2.3 Study population

Routine clinical investigations, including microbiological sampling, were conducted at the discretion of the treating clinical team. In addition, patients were assessed for symptom prevalence and functional activity weekly for 9 weeks, whilst formal spirometry was conducted (at discharge, 6-weeks, and 9-weeks). Patients were assessed using a combination of hospital review, telephone consultation, and patient diaries.

A five-item, CAP specific questionnaire was used to record patient-reported symptoms prior to discharge and at each follow-up consultation.[209] Dynamic spirometry (forced expiratory volume in 1 second; FEV_1 and Forced Vital Capacity; FVC) was assessed using a handheld spirometer (MicroPlus; Micro Medical, Buckinghamshire, UK) in accordance with published guidelines.[283] Briefly, all measures were initiated from total lung capacity (TLC) and exhaled maximally until they reached residual volume (RV). Participants completed a minimum of three efforts, each separated by a minimum of 30 seconds rest. A hand-held mouth pressure meter (Micro R.P.M., Micro Medical, Buckinghamshire, UK) was used to assess both maximal inspiratory (MIP) and maximal expiratory (MEP) mouth pressure. Inspiratory manoeuvres were measured during quasi-static contractions (Mueller manoeuvre) that were initiated from RV, participants were instructed to contract the inspiratory muscles forcefully during each manoeuvre and all efforts were accompanied with motivation and sustained for at least 2 seconds. Similarly, MEP measures were initiated from TLC total lung capacity and participants were instructed to exhale forcefully for no longer than 3 seconds. Both inspiratory and expiratory

efforts were separated by 30 seconds and repeated until serial measures were within 10% or 10 cmH2O of one another with the highest value recorded for analysis

Participants were provided with an IMT device (POWERbreatheKHP2, HaB International, Southam, UK) for a period of nine weeks. Throughout the intervention period participants conducted two IMT sessions daily at an intensity equivalent to 50% of the participants MIP. After consultation and critical review by members of PPI group, session volume was incremental across the intervention; participants started with 10 breaths per session in week one, increasing to 20 breaths in week two, and to a maintenance volume of 30 breaths for weeks three to nine. This protocol provided an IMT habituation period of two weeks followed by an intervention period of seven weeks which was agreed in collaboration with members of Nottingham Pneumonia Patient and Public Involvement Group. Training breaths and training load were recorded in a daily participant diary.

7.2.4 Outcome measures

The primary outcome measures of interest were; a) IMT safety assessed by frequency and severity of patient reported IMT side effects (graded according to Common Terminology Criteria for Adverse Events (CTCAE, version 4.3, June 2010, Table 7.1), and monitoring of adverse events; and b) IMT tolerability, measured by proportion of patients who completed IMT training according to study protocol until completion. Compliance with study protocol was defined as

training twice daily at 50% PImax and specified volume (determined by the stage of intervention) for a full 9 weeks of study follow-up.

Secondary outcomes of interest were; a) trajectory of patient-reported symptoms (CAP score, comparing mean CAP score at discharge and last recorded CAP score); and b) markers of pulmonary and respiratory muscle function (comparing mean FEV1.0, FVC, MIP, and MEP at discharge and 9-week follow-up.)

Table 7-1: Common Terminology Criteria for Adverse Events scale

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate - 2 Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE.

Activities of Daily Living (ADL)

**Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*

***Self-care ADL refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.*

7.2.5 Statistical methods

Descriptive statistics were used to summarise patient characteristics. Mean and standard deviation, or median and inter-quartile ranges were calculated for continuous data; absolute number and proportions were calculated for categorical data. Paired t-tests were used to test significance of difference between means at baseline and follow-up (last recorded measurement for patients failing to complete training per protocol or 9-week follow-up, as appropriate).

Statistical analyses were conducted using Stata/IC 15 (©StataCorp. 2017)

7.3 Results

7.3.1 Study population

Between March 2017 and April 2018, 46 patients were identified as eligible for study enrolment (Figure 7.1). After clinical review, 22 patients were recruited into the study. Baseline characteristics of patients are presented in Table 7.2. The average age of recruited patients was 55.2 years (range 27.9-77.3) and 16 (72.7%) were male. One or more co-morbid illness was present in 10 (45.5%) patients. World Health Organisation (WHO) performance status at hospital admission was grade 1 in nine, grade 2 in three, grade 3 in seven, and grade 4 in three patients. Twelve patients reported having never smoked, four were ex-smokers, and six were current smokers. Most patients were admitted to hospital from the Emergency Department (21/22), and three patients had been prescribed oral antibiotics prior to hospital admission. Unilobar consolidation was the commonest radiographic abnormality identified on admission chest x-ray (17/22 patients), followed by multilobar consolidation (4/22) and unilateral pleural effusion in a single patient. Sixteen patients had a repeat chest x-ray within 9-weeks of discharge, with complete radiographic resolution in 14, persistent consolidation in one patient, and a unilateral pleural effusion in another.

Figure 7-1; IMT Study flow diagram

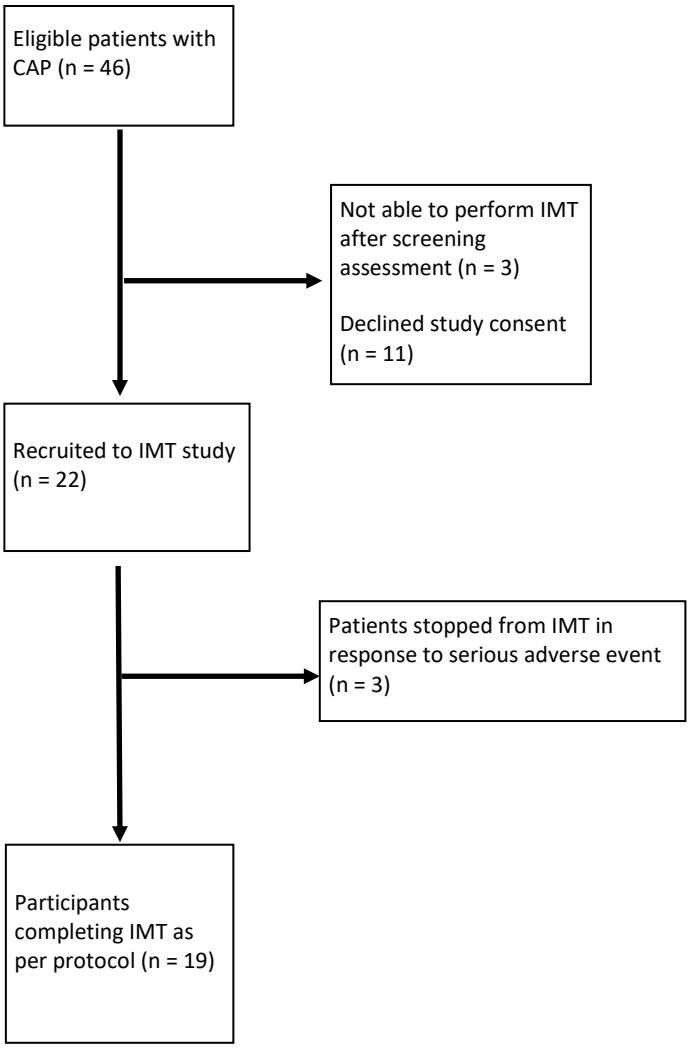


Table 7-2; IMT Study Patient characteristics

Mean Age (range)	**55.2 (27.9 – 77.3)**	
Gender, male (%)	16 (72.7)	
Co-morbid disease, n (%)		
0	12 (54.6)	
1	6 (27.3)	
≥2	4 (18.1)	
Hypertension	5 (22.7)	
Dyslipidemia	3 (13.6)	
Cerebrovascular disease	2 (9.1)	
Congestive Cardiac Failure	2 (9.1)	
Asthma	1 (4.5)	
Diabetes Mellitus	1 (4.5)	
Neoplasia	1 (4.5)	
Smoking status, n (%)		
Never Smoker	12 (54.6)	
Ex-Smoker	4 (18.2)	
Current Smoker	6 (27.2)	
Performance status, n (%)	6-weeks prior to admission	Hospital admission
0	18 (81.8)	0
1	4 (18.2)	9 (40.9)
2	0	3 (13.6)
3	0	7 (31.8)
4	0	3 (13.6)

7.3.2 Primary outcome

One unexpected, unrelated serious adverse event (SAE) occurred during study follow-up. A participant who had completed 8 weeks of study follow-up per protocol, unexpectedly and rapidly deteriorated and subsequently died. The participant had demonstrated progressive improvement in CAP scores and reported increasing functional recovery towards baseline during follow-up. At clinical review at 6-weeks post-discharge observations were normal, examination was unremarkable, and a repeat plain chest radiograph demonstrated complete resolution of consolidation.

Three participants under active follow-up at the time of SAE were contacted by telephone and instructed to stop IMT pending further instruction. These participants did not restart IMT as they were outside of the training window at the time of conclusion of the investigation. It was decided that they were not eligible for inclusion in the analysis of protocol compliance. Two participants who were lost to follow-up at day 7 and day 14 were included in the analysis based on available data.

Inspiratory muscle training was completed according to study protocol in 14/19 (73.7%) patients, with three patients who were stopped from IMT by the study sponsor at the time of SAE investigation being excluded from analysis of protocol compliance. Side effects from IMT were reported on 15 occasions (10 individuals) across the 22 participants over a total of 1183 training days (range of training days 7 to 63). Side effects related to IMT included chest pain (x2), cough (x1), increased dyspnoea (x4), and dizziness (x8). Participants rated these side

effects as grade 1 on CTCAE scale; they did not prevent patients from completing the current session or continuing with future training.

7.3.3 Secondary outcomes

Patient-reported CAP scores improved between baseline (mean 44.3 ±19.6) and last recorded measurement (mean 88.2 ±15.0), with a significant average improvement of 43.9 (difference between means, 95% CI 34.8-52.9, $p < 0.001$, Figure 7.2 and Table 7.3). All spirometry measures improved significantly between baseline assessment at discharge and repeat assessment at 9-weeks (see Figure 7.3 and Table 7.4).

Figure 7-2: Patient reported symptoms (CAP score) in patients participating in daily inspiratory muscle training following discharge from hospital for community-acquired pneumonia.

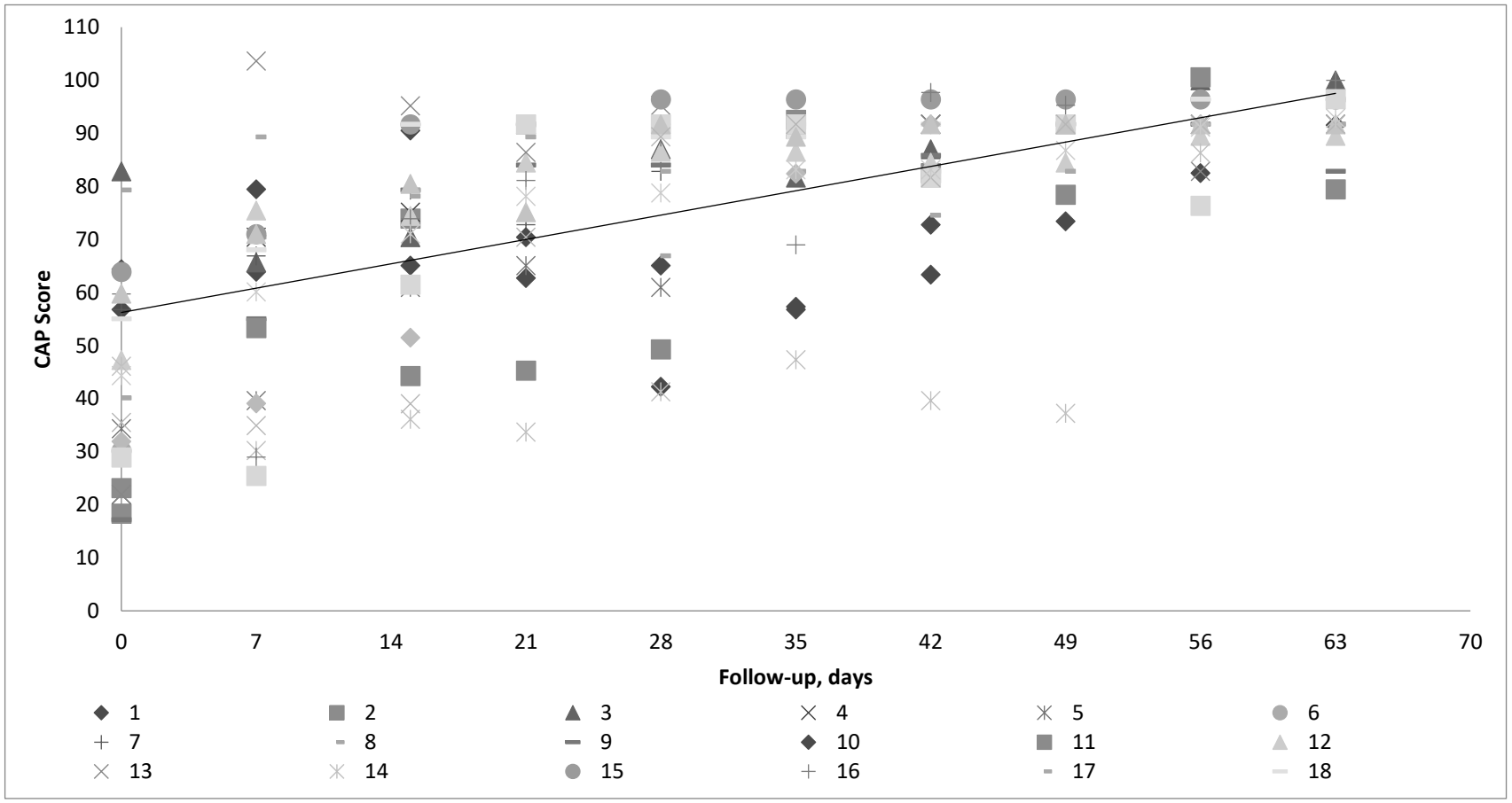


Table 7-3: Table of individual patient CAP scores at discharge, 6-weeks, and 9-weeks for IMT study participants

Participant	CAP score									
	Discharge	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 56	Day 63
1	56.8	63.9	65.1	62.7	65.1	56.8	72.8			
2	18.3		74.0							
3	82.8	65.7	70.4	91.7	87.0	81.7	87.0	91.7	100.0	100.0
4	21.9	70.4	75.1	91.7	91.7	91.7	91.7	91.7	91.7	91.7
5	34.3	39.6	60.9	65.1	60.9	91.7	91.7	91.7	91.7	91.7
6	30.2									
7	56.8	66.9	79.3	72.8	82.8	91.7	82.8	91.7	96.4	96.4
8	79.3	70.4	78.1	91.7	66.9	91.7	74.6	91.7	91.7	91.7
9	17.2	55.0	79.3	84.0	84.0	89.3	85.8	91.7	91.7	82.8
10	64.4	79.5	90.5	70.4	42.3	57.3	63.4	73.4	82.5	91.5
11	23.1	53.3	44.3	45.3	49.3	92.5	82.5	78.5	100.6	79.5
12	47.3	75.4	74.4	84.5	86.5	86.5	84.5	84.5	89.5	89.5
13	21.9	103.6	95.2	86.4	95.3	91.7	91.7	91.7	82.8	96.4
14	46.1	30.2	36.1	33.7	41.3	47.3	39.6	37.2	86.3	91.7
15	63.9	71.0	91.7	91.7	96.4	96.4	96.4	96.4	96.4	96.4
16	59.7	29.0	73.9	81.1	89.3	69.0	97.7	95.3	91.7	100.0
17	40.1	89.3	79.2	89.3	82.8	82.8	82.8	82.8	91.7	91.7
18	55.0	68.0	91.7	91.7	89.3	89.3	91.7	91.7	96.4	96.4
19	31.9	39.1	51.5	91.7	91.7	82.4	91.7	91.7	91.7	96.4
20	28.9	25.4	61.5	91.7	91.7	91.7	81.7	91.7	76.3	96.4
21	59.8	71.0	80.5	75.1	91.7	89.3	91.7	91.7	91.7	91.7
22	35.5	34.9	39.1	70.4	89.3	91.7	81.7	91.7	91.7	91.7
Mean	44.3	57.2	71.0	78.1	78.8	83.1	83.2	86.8	91.2	92.8

Table 7-4: Table of mean FEV1.0, FVC, MIP, and MEP at discharge, 6-weeks, and 9-weeks for IMT study participants

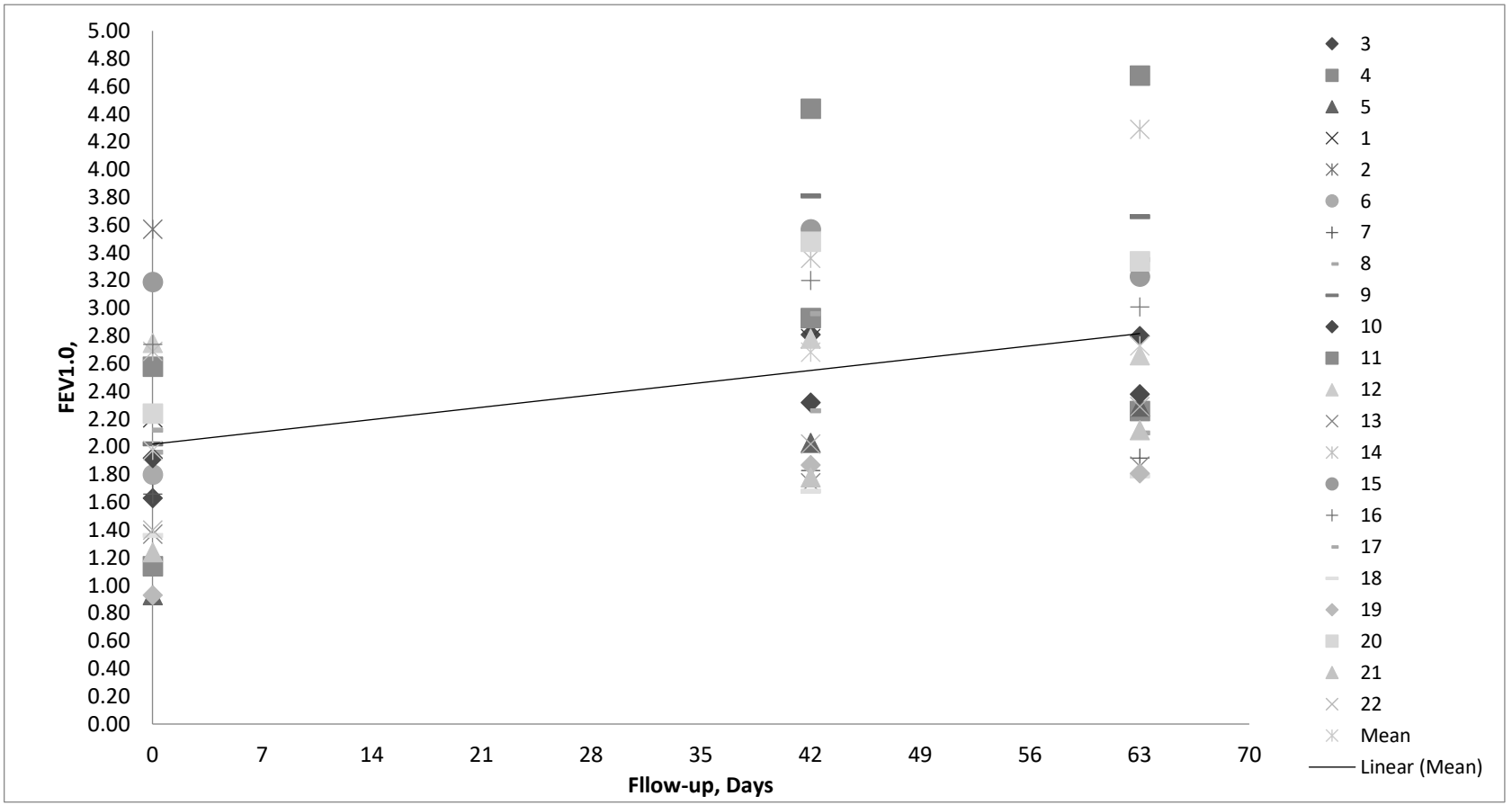
	Discharge (n=22)	6-week follow-up (n= 20)	9-week follow-up (n = 19)	Difference in mean between hospital discharge and 9-week follow-up (95% CI)	p value
FEV1.0	1.89	2.68	2.73	0.84 (0.54-1.14)	<0.001
FVC	2.27	3.22	3.18	0.91 (0.56-1.27)	<0.001
MIP	65.2	102.9	116.0	50.8 (37.7-64.0)	<0.001
MEP	74.4	100.8	105.6	31.2 (18.0-44.4)	<0.001

FEV1.0 = forced expiratory volume in 1 second, FVC = forced vital capacity, MIP = mouth maximal inspiratory pressure, MEP = mouth maximal expiratory pressure, 95% CI = 95% confidence interval.

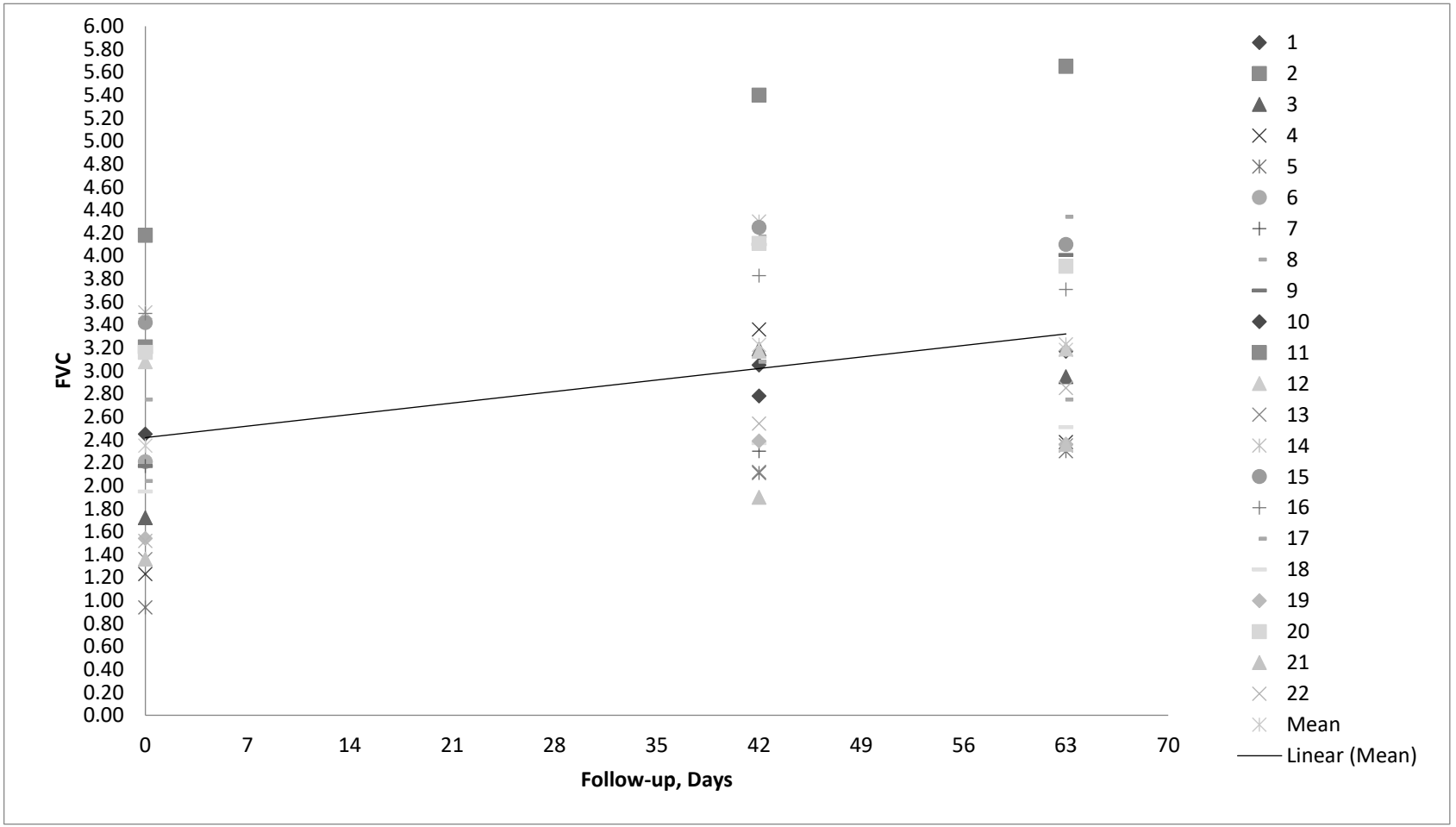
** p value compares difference in means at discharge versus 9 weeks*

Figure 7-3: Pulmonary function measurements in IMT study participants

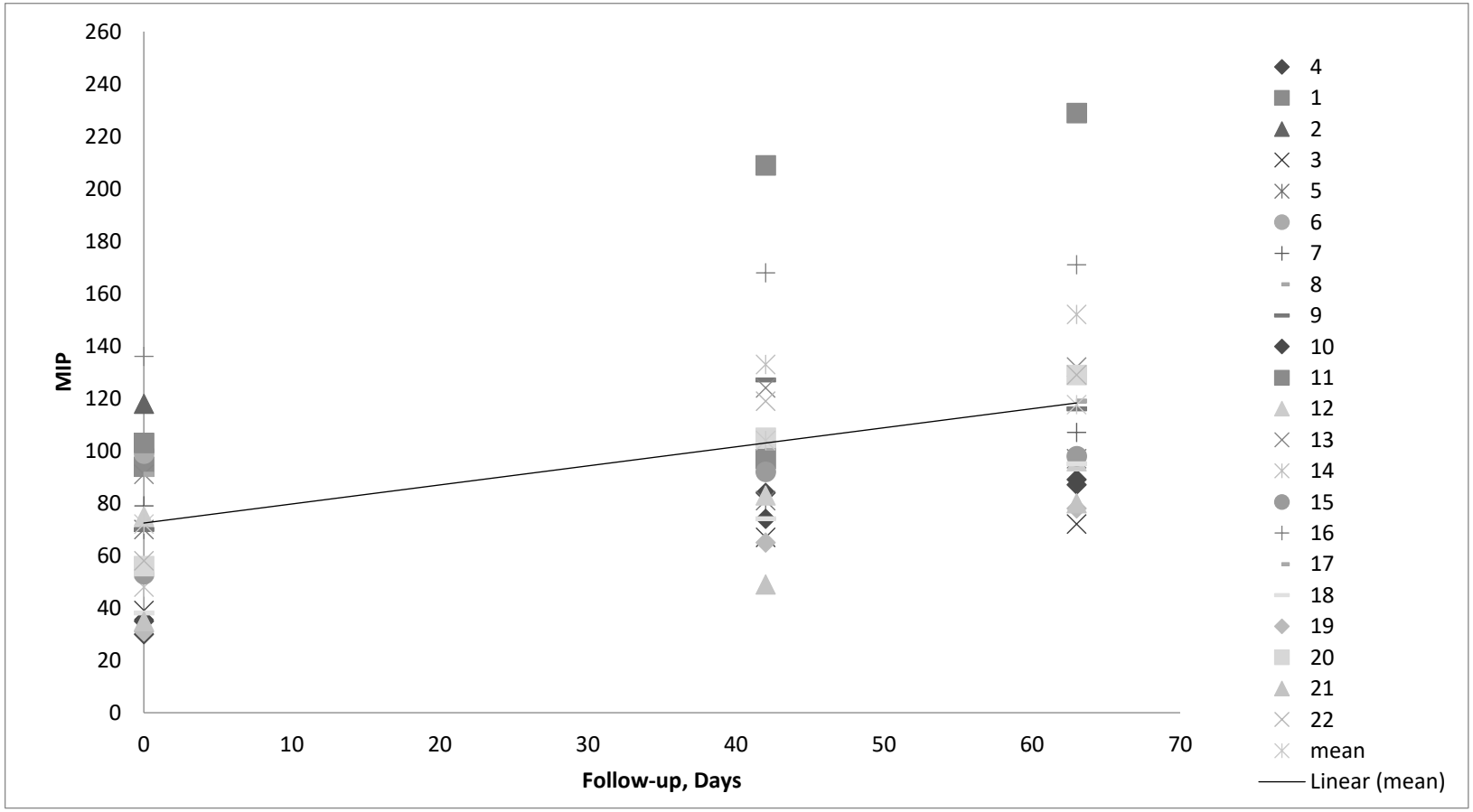
A) FEV1.0



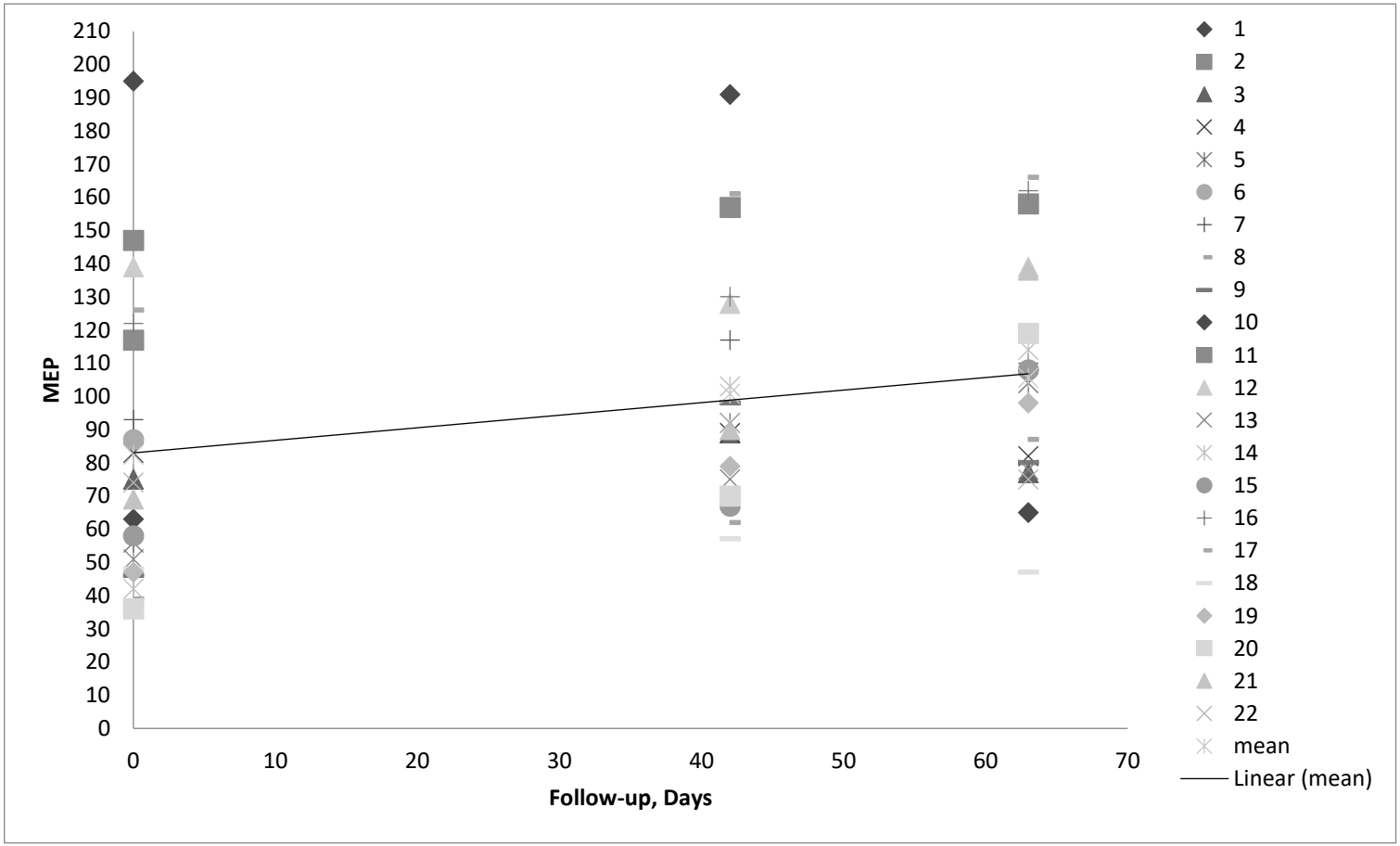
B) FVC


FVC
6.00
5.80
5.60
5.40
5.20
5.00
4.80
4.60
4.40
4.20
4.00
3.80
3.60
3.40
3.20
3.00
2.80
2.60
2.40
2.20
2.00
1.80
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
0
7
14
21
28
35
42
49
56
63
70
Follow-up, Days
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
Mean
Linear (Mean)

C) MIP


260
240
220
200
180
160
140
120
100
80
60
40
20
0
MIP
0
10
20
30
40
50
60
70
Follow-up, Days
4
1
2
3
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
mean
Linear (mean)

D) MEP


MEP
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
Follow-up, Days
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
mean
Linear (mean)

7.4 Discussion

This is the first study of IMT in adult patients recovering following hospitalisation with an episode of CAP. We report that IMT is tolerable in these patients, but IMT efficacy is yet to be determined. A randomised controlled trial of IMT in CAP recovery is needed.

Patients recovering following an episode of CAP found IMT to be acceptable and tolerable. Over 1183 patient-days, side-effects related to IMT were reported rarely. All the IMT attributable side-effects were low severity, rated as grade 1 on CTCAE scale, and did not prevent further training or deviation from the study protocol. This is consistent with results from studies of IMT in different patient cohorts. In a study of IMT in patients with thoracic malignancy only 3 patients reported IMT-related side effects during follow-up, [280] whilst two studies of patients with cardiovascular disease reported no adverse events during IMT (pre-operative IMT in patients undergoing coronary artery bypass grafting and IMT in chronic heart failure).[279]

On repeated assessment patients reported that they believed IMT was helpful in their recovery. Patients have reported similar opinions in other studies of IMT; pre-operative patients[278] and patients with chronic heart failure participating in rehabilitation[279] also reported that IMT was tolerable and that they believed it to be beneficial in their recovery.

Patient-reported symptoms and functional impairment are common in recovery following an episode of CAP,[86] improving with increasing time after initial admission. We observed improvement in CAP-symptom scores and pulmonary

function tests over the course of follow-up. These improvements would be expected in 'normal recovery' in patients not using an IMT device. This study cannot determine the extent to which IMT may have influenced the rate or extent of improvement due to its methodology; a small feasibility study, without a control group, and no randomisation procedures or blinding of patients or researchers.

7.4.1 Serious Adverse Event

One participant experienced a SAE (serious adverse event, death) which was fully investigated internally and externally as follows. On notification of SAE the study team completed appropriate immediate actions to ensure safety of the remaining study participants, as per study protocol for SAEs. The study sponsor was immediately contacted and informed verbally of the SAE. Three participants under active follow-up at the time of SAE were contacted by telephone and instructed to stop IMT pending further instruction. Contemporaneous notes were recorded throughout the investigation process. A formal written report was completed and submitted to study sponsor within 24 hours outlining available details of events and action taken. An additional report was submitted to Nottingham Research Ethics Committee within 7 days of SAE.

I completed an extensive literature review covering studies of patients and healthy volunteers participating in IMT studies to determine if any IMT-related fatalities had previously been reported. This search identified 140 primary studies of inspiratory muscle training, with no reported IMT-related fatalities identified after full-text review. An independent, external investigation was commissioned by the study sponsor. After reviewing the study protocol, manufacturer's product literature, and details of the SAE, the independent reviewer determined that the SAE was unexpected and unrelated to IMT.

The participant had completed IMT per protocol until their unexpected and acute deterioration and had been observed to improve over the course of their follow-up as demonstrated by; a reduction in patient-reported symptoms (CAP

score), improving pulmonary function tests, increased exercise capacity, and radiographic resolution of consolidation. The extensive independent review determined that the SAE was unrelated to IMT, consistent with the results of a systematic literature review of IMT which did not identify any studies in patients or healthy volunteers reporting IMT-related fatalities. The cause of death was determined at post-mortem to be an acute myocardial infarction. A coroner's report was completed by the clinical team caring for the patient, and the coroner's office agreed with the post-mortem finding of cause of death without further investigation.

There is increasing evidence that patients are at significantly increased risk of developing a cardiovascular event (CVE) following an episode of CAP, and that this increased risk persists long beyond apparent clinical recovery.[205,284,285]

7.4.2 Strengths and Limitations

This is the first study of IMT in patients recovering following an episode of CAP; a group of patients that experience a significant burden of disease in recovery which impacts quality of life and functional status. The study was designed with extensive input from patients, influencing the frequency and intensity of training regimen, introducing a habituation phase, and determining the extent and frequency of follow-up. This ensured acceptability to patients who consented to participate in study and is reflected in the level of protocol compliance.

One limitation is an assumption that inspiratory muscle weakness is a contributing factor in the persistence of symptoms and functional impairment following an episode of CAP. To our knowledge, there have not been any

physiological studies in patients with acute lower-respiratory tract infections to determine if inspiratory muscle, and specifically diaphragmatic weakness, is a contributory pathophysiological factor. However, the investigations that would need to be performed to determine this are invasive, requiring placement of pressure probes in the distal oesophagus and stomach, and which would be very poorly tolerated by patients in the acute phase of recovery following an episode of CAP. Therefore, it is acceptable to adopt a pragmatic approach and use the measurement of MIPs in combination with IMT in patients to determine if there is benefit, and then attribute any observed improvement to increased respiratory muscle strength / function.

7.4.3 Implications

This exploratory study has demonstrated that IMT is tolerable in adult patients recovering following hospitalisation with CAP. Further research to determine IMT efficacy in these patients is required. The potential benefits of IMT may include shorter duration or severity of symptoms and reduced functional impairment above that observed during 'unaided' recovery, but these need to be evaluated against the low-grade side-effects experienced by patients during IMT.

Chapter 8: Discussion

This chapter will discuss the results of the thesis, associated implications, and suggested future research according to the two prevailing themes pneumococcal serotype trend and CAP recovery.

8.1 Summary of results

8.1.1; Pneumococcal CAP

The thesis demonstrates that the incidence of pneumococcal CAP increased between 2013 and 2018 based on the data obtained from a large UK teaching hospital, predominantly due to increases in serotype three and NVT-serotypes, concurrent with an increase in the incidence of all cause CAP. Community-acquired pneumonia due to PCV13-serotypes remains more likely in pneumococcal clinical risk groups; however, PPV23-serotype pneumonia is more likely in younger patients outside of these traditional risk groups.

8.1.2; Community-acquired pneumonia recovery

Studies included in this thesis have demonstrated that patients experience substantial levels of morbidity following an episode of CAP; persistent and intrusive symptoms, impaired functional activity, and high 30-day re-consultation rates. Patients report feeling unprepared for the degree of symptom persistence and levels of functional impairment, expressing high levels of anxiety, vulnerability, and impaired quality of life. Fatigue is reported as particularly intrusive and persistent, but CAP specific measures of fatigue are lacking. A cohort study of IMT in these patients demonstrated that IMT is both tolerable and acceptable for patients, but IMT efficacy in this patient population is yet to be determined.

Furthermore, one in ten patients discharged from hospital after an episode of CAP are readmitted within 30 days, with cardiovascular events accounting for 1/3rd of these readmissions. The presence of co-morbid disease, low socio-economic status, and clinical instability at discharge were identified as risk factors for readmission, yet these are inconsistently assessed. In the pilot study exploring the optimum method and timing of assessment across several clinically important domains in CAP recovery, baseline assessment at discharge followed by re-assessment and comparison at 6 weeks demonstrated the optimum balance between patient tolerability and acceptability whilst continuing to inform decisions.

8.2 Implications

8.2.1; Pneumococcal CAP

Firstly, the continued immunisation of at-risk populations, in accordance with UK vaccination policy, will exert vaccine-pressure on pneumococcal serotypes that, based on existing evidence, is likely to contribute to serotype shift and continue the trend for an increase in NVT-serotypes.

Secondly, NVT-serotypes are more likely to affect younger patients outside of previous pneumococcal risk groups, with implications for front-line clinicians managing these patients and for vaccine policy.

Thirdly, vaccine manufacturers require contemporaneous serotype data to inform the prevalent serotypes causing disease and which should be included in vaccines. Due to the limited number of serotypes currently able to be included in the available vaccines, either new higher-valency vaccines need to be developed

or existing vaccine need to have less prevalent serotypes substituted and replaced with emerging serotypes.

8.2.2; Community-acquired pneumonia recovery

The outlined body of work in CAP recovery has provided a valuable insight for patients, their relatives and carers, and healthcare professionals into the burden of disease experienced following an episode of CAP. Taken together, the results provide a summary of the expected course of recovery, including symptom persistence, impact upon activities of daily living and occupation, and rates of readmission and associated risk factors. The potential uses of this information are several folds.

First, it can be used as a basis to inform discussions between healthcare professionals and their patients about the expected course of recovery, including average timeframes for symptom resolution, return to activity, and return to work.

Second, information leaflets, websites, mobile applications, and other multimedia resources can be generated to provide additional sources of information.

Third, increasing the awareness and knowledge of healthcare professionals regarding the substantial burden of disease experienced in recovery, and the fact that this is normal, will increase confidence of healthcare professionals when counselling patients, including preventing unnecessary antimicrobial prescriptions and readmissions to hospital.

Fourth, by highlighting the disparity between patient reported outcome measures and physician or radiology-assessed recovery, healthcare professionals will be educated and empowered to consider and assess those outcomes which most matter to patients, namely symptom resolution, quality of life, and return to normal function.

8.3 Future Research

8.3.1; Pneumococcal CAP

Continued surveillance of serotype trends for both invasive pneumococcal disease and pneumococcal CAP is warranted to inform both vaccine policy and clinical practice. Research is required to further develop assays capable of determining clinically important and emerging pneumococcal serotypes from non-invasive samples.

8.3.2; Community-acquired pneumonia recovery

The included body of work, in addition to previous studies, has demonstrated the substantial burden of disease experienced by patients during CAP recovery as well as the wider economic and health system implications. Future studies in CAP recovery are required to address several clinically important questions;

1) What is the normal or average course of recovery following an episode of hospitalised CAP?

2) What are the risk factors that can predict impaired or delayed recovery?

3) What interventions can be employed to expedite and/or assist patients during recovery?

To answer these questions, a multi-centre observational cohort study recruiting enough patients hospitalised with CAP is required. This study should incorporate a nested qualitative study to capture which outcomes are important to patients and to further assess which assessments (tools used and timing) are most acceptable and tolerable. It is also recommended that such a study employ the assessments outlined in table 8-1, which have been recommended based on the work presented in this thesis in conjunction with research in COVID-19 follow-up. These assessments should be conducted at discharge (including a retrospective assessment of functional activity and symptoms, based on patient recall 6 weeks prior to acute episode), at 3-, 6-, and 12-months post-discharge.

Table 8-1: Suggested assessment tools to be included in future studies of CAP recovery

Domain	Tool
Symptoms	CAP-symptom score
Fatigue	MFIS
	FACIT
Depression	PHQ9
Cognition	MoCA
Anxiety	GAD7
Functional activity	EQ5D-5L
Exercise capacity	6MWT
	Incremental shuttle walk test
Pulmonary function	FEV1.0, FVC, PEFR

Once ‘normal’ or ‘average’ recovery has been defined, research to identify targets and to develop interventions to reduce the morbidity experienced by patients is required. It is recommended that these should include;

1) Randomised controlled trials comparing an IMT device against a sham device to determine IMT efficacy in patients recovering following an episode of CAP
2) Randomised controlled trials comparing multimodal packages of support following discharge against standard follow-up (chest x-ray at 6-8 weeks)

These studies should incorporate the recommended assessment tools outlined in Table 8-1, with follow-up extending to at least 12 months. When determining primary outcomes of interest, patient-reported outcome measures should be employed.

8.4 Conclusion

8.4.1; Pneumococcal CAP

In conclusion, in both invasive and non-invasive pneumococcal disease an up-to-date understanding of prevailing pneumococcal serotypes and the associated ‘at risk’ populations are fundamental to inform vaccine development, immunisation policy, and clinical practice. Surveillance studies to gather this vital information are warranted.

8.4.2; Community-acquired pneumonia recovery

Patients experience a substantial burden of disease during their recovery following an episode of CAP, with high rates of readmission and reconsultation. Studies to define CAP recovery in greater detail are required, including studies to

derive and validate risk assessments for impaired recovery, and to determine potential targets for novel interventions to alleviate / expedite recovery. Future studies should draw on previous studies of CAP recovery as well as the recent studies of recovery following COVID-19 infection.

Appendix 1; Data extraction form for systematic review of patient reported outcome measures in CAP recovery

Reviewer			
Trial ID Number		Year of publication	
Lead Author			
Journal			
Description / Comments			
Abstract Only ☐	Full paper ☐		
English ☐	Other language		
Study Details			
Type of Study	Prospective ☐	Retrospective ☐	
	RCT ☐	Cohort ☐	Case -control ☐
	Cross-sectional ☐	Other ☐	
Country			
Number of Centres			
Type of Centres			
Enrolment Period			
Follow-up Period			

Participant Details			
Inclusion Criteria			
Exclusion Criteria			
	CAP	N / Controls	Notes
Average Age			
Male: Female Ratio			
Number Identified			
Number Enrolled			
Number lost to follow-up			
Final Study Number			
CAP Severity Number / proportion	PSI.		CURB65.
Outcomes / Results			

Symptoms at any time point within 90 days of discharge	Number and / or proportion with persistent symptom	
	Cough	
	Dyspnoea	
	Chest Pain	
	Sputum	
	Fatigue	
	other	

CAP Symptom score at any time point within 90 days of discharge	Either CAP symptom score or change in CAP symptom score or average time for normalisation of CAP symptom score	

Functional at any time point within 90 days of discharge	Number and / or proportion returning to functional activity	
	Return to work	
	Return to ADLs	

Quality of Life Questionnaire at any time point within 90 days of discharge	Average change in quality-of-life score at 4-6 weeks (28-42 days) post-discharge	
	SF-8	
	SF-36	
Physician rated cure at any time point within 90 days of discharge	Number and / or proportion recorded with physician rated clinical cure at 4-6 weeks (28-42 days) post-discharge	
	Clinical cure	
Healthcare Utilisation @ Any time point up to 90 days	Number and / or proportion utilising	
	Readmission	
	Emergency Department Attendance	
	GP Consultation	
	Antibiotic Prescription	

Study Quality	
Defined study population? (* Clear CAP definition, adults, eligibility criteria documented)	Yes / No
Defined and documented study period?	Yes / No
Study sample representative of population? (* Sample population characteristics documented, free from sampling bias, representative of general population)	Yes / No
Loss to follow-up documented and number appropriate. (* >80% of enrolled participants completing study)	Yes / No
Clearly defined outcome measure? (* Primary and secondary outcomes defined, justified and appropriate)	Yes / No
Defined follow-up period? (* The optimum timing of follow-up in recovery is not known)	Yes / No

Reviewer's Comments:		
References reviewed for relevant associated articles	Yes	☐
Contact authors for further details?	Yes	☐

Appendix 2; Data extraction form for systematic review of readmission and risk

☐ Included ☐ Excluded ☐ Double checked

Reviewer			
Trial ID Number		Year of publication	
Lead Author			
Title			
Journal			
Description / Comments			
Abstract Only ☐		Full paper ☐	
English ☐		Other language	
Study Details			
Type of Study	Prospective ☐	Retrospective ☐	
	RCT ☐ Cohort ☐ Case -control ☐ Cross-sectional ☐ Other ☐		
Country			
Number of Centres			
Type of Centres			
Enrolment Period			
Follow-up Period			

Participant Details			
Inclusion Criteria			
Exclusion Criteria			
	CAP	N / Controls	Notes
Average Age			
Male: Female Ratio			
Number Identified			
Number Enrolled			
Number lost to follow-up			
Final Study Number			
CAP Severity Number / proportion	PSI;		CURB65;
Length of hospital stay (LOS)	Days		Notes

Readmission rate	Number and/ or proportion
30 days readmission rate	
Optional:	
60 days readmission rate	
90 days readmission rate	

Reasons for hospital readmissions	Number/ and or proportion	Additional Information
Pneumonia related		
Non- pneumonia related		
i. cardiovascular	`	

Combined (both pneumonia and non- pneumonia related		

Type of Measurement	Odds Ratio	Risk Ratio	Hazard Ratio	Rate Ratio
Adjusted				
Unadjusted				

Risk factors for readmissions	Value	Confidence Intervals

Study Quality	
Defined study population? (* Clear CAP definition, adults, eligibility criteria documented)	Yes / No
Defined and documented study period?	Yes / No
Study sample representative of population? (* Sample population characteristics documented, free from sampling bias, representative of general population)	Yes / No
Loss to follow-up documented and number appropriate. (* >80% of enrolled participants completing study)	Yes / No
Clearly defined outcome measure? (* Primary and secondary outcomes defined, justified and appropriate)	Yes / No
Defined follow-up period? (* The optimum timing of follow-up in recovery is not known)	Yes / No
Adjusted measurements of risk factors for hospital readmission? (* Are the values adjusted for possible cofounders?)	Yes / No
Research funding and conflict of interest clearly stated?	Yes/ No
Total number of points	/8

Reviewer's Comments:
References reviewed for relevant associated articles Yes ☐
Contact authors for further details? Yes ☐

Appendix 3; Ethics approval forms

a) Pneumococcal serotype trends, surveillance and risk factors in UK adult pneumonia, 2013-2018;

NHS
Health Research Authority

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

Email: hra.approval@nhs.net

10 August 2017

Dear Dr Lim

Letter of HRA Approval for a study processed through pre-HRA Approval systems

Study title:	**A Population based prospective cohort study of pneumococcal pneumonia in adults following the introduction of childhood pneumococcal vaccination in the UK**
IRAS project ID:	**201344**
Sponsor	**Nottingham University Hospitals NHS Trust**
Amendment number:	**Non-substantial amendment - 27/06/2017**
Amendment date:	**27/06/2017**

Thank you for your request to bring the above referenced study, processed under pre-HRA Approval systems, under HRA Approval.

I am pleased to confirm that the study has been given **HRA Approval.** This has been issued on the basis of an existing assessment of regulatory compliance, which has confirmed that the study is compliant with the UK wide standards for research in the NHS.

The extension of HRA Approval to this study on this basis allows the sponsor and participating NHS organisations in England to set-up the study in accordance with HRA Approval processes, with decisions on study set-up being taken on the basis of capacity and capability alone.

Please note that the amendment submitted to bring this study under HRA Approval (referenced above) is also approved by issue of this letter. You should not expect anything further from the HRA regarding the amendment. If the submitted amendment included the addition of a new NHS organisation in England, the addition of the new NHS organisation is also approved and should be set up in accordance with HRA Approval processes (e.g. the

organisation should be invited to assess and arrange its capacity and capability to deliver the study and confirm once it is ready to do so).

Participation of NHS Organisations in England

Please note that full information to enable set up of participating NHS organisations in England is not provided in this letter, on the basis that activities to set up these NHS organisations is likely to be underway already.

The sponsor should provide a copy of this letter, together with the local document package and a list of the documents provided, to participating NHS organisations in England that are being set up in accordance with HRA Approval Processes. It is for the sponsor to ensure that any documents provided to participating organisations are the current, approved documents.

For non-commercial studies the local document package provided to NHS organisations should include an appropriate Statement of Activities and HRA Schedule of Events. The sponsor should also provide the template agreement to be used in the study, where the sponsor is using an agreement in addition to the Statement of Activities. Participating NHS organisations in England should be aware that the Statement of Activities and Schedule of Events for this study have not been validated by the HRA, but the HRA expects that the sponsor provides these to participating NHS organisations. Any changes that are appropriate to the content of the Statement of Activities and Schedule of Events should be agreed in a pragmatic fashion as part of the process of assessing, arranging and confirming capacity and capability to deliver the study.

For commercial studies the local document package should include a validated industry costing template and the template agreement to be used with participating NHS organisations in England.

It is critical that you involve both the research management function (e.g. R&D office and, if the study is on the NIHR portfolio, the LCRN) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

If subsequent NHS organisations in England are added, an amendment should be submitted to the HRA.

After HRA Approval

In addition to the document, *"After Ethical Review – guidance for sponsors and investigators"*, issued with your REC Favourable Opinion, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA

- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval.

The HRA website also provides guidance on these topics and is updated in the light of changes in reporting expectations or procedures.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-rec-for-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website (http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/).

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/.

Your IRAS project ID is 201344. Please quote this on all correspondence.

Yours sincerely

Elizabeth Bottomley
Application Administrator

Email: hra.approval@nhs.net

b) Experiences, concerns, and needs in recovery from Community-Acquired Pneumonia – a qualitative interview study of patients and healthcare professionals;

17 RMOC7

NHS
Health Research Authority

Professor Wei Shen Lim
Consultant Respiratory Physician + Honorary Professor of Medicine
Nottingham University Hospital NHS Trust
Respiratory Medicine, David Evans Building
City Hospital Campus
Hucknall Road Nottingham
NG5 1PB

Email: hra.approval@nhs.net

25 May 2017

Dear Professor Lim

Letter of HRA Approval

Study title:	**Patient Experience of Recovering from Pneumonia - A Qualitative Longitudinal Interview Study**
IRAS project ID:	**218533**
REC reference:	**17/SW/0087**
Sponsor	**Nottingham University Hospital NHS Trust**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators"*, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at: http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-rec-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **218533**. Please quote this on all correspondence

Yours sincerely,

Natalie Wilson

Assessor

Email: hra.approval@nhs.net

Copy to: *Ms Deborah Ashton, Nottingham University Hospitals NHS Trust, Sponsor contact*
Dr Natalie McGregor, Nottingham University Hospitals NHS Trust, Lead NHS R&D contact

Appendix A - List of Documents

The final document set assessed and approved by HRA Approval is listed below.

Document	Version	Date
Covering letter on headed paper		22 March 2017
GP/consultant information sheets or letters	1.0	19 January 2016
Interview schedules or topic guides for participants [Patient]	1.0	15 November 2016
Interview schedules or topic guides for participants [HCP]	1.0	17 January 2017
IRAS Application Form [IRAS_Form_22032017]		22 March 2017
IRAS Checklist XML [Checklist_22032017]		22 March 2017
IRAS Checklist XML [Checklist_08052017]		08 May 2017
Other [CV - Dr Harry Pick]	NA	05 May 2016
Other [CV - Dr Manpreet Bains]	NA	
Other [CV - Deborah Ashton]	NA	
Other [Statement of Activities]	1	08 May 2017
Other [Schedule of Events]	1	08 May 2017
Other [REC Response]	NA	05 May 2017
Participant consent form [Patient]	1.0	22 December 2016
Participant consent form [HCP]	1.0	22 December 2016
Participant information sheet (PIS) [Patient]	V1.1	28 April 2017
Participant information sheet (PIS) [HCP]	1.0	22 December 2016
Research protocol or project proposal [Research Protocol]	V1.1	12 April 2017
Summary CV for Chief Investigator (CI)		01 December 2016
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Flowchart]	1.0	16 January 2017
Validated questionnaire [CAP Score Questionnaire]		

c) Assessing recovery following an episode of Community-Acquired Pneumonia – an exploratory study;

NHS
Health Research Authority
West Midlands - Solihull Research Ethics Committee
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Please note: This is an acknowledgement letter from the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

15 May 2018

Dr Harry Pick
Respiratory Infection Research Group
Room B02, Clinical Sciences Building
Nottingham City Hospital, Hucknall Road
NG5 1PB

Dear Dr Pick

Study title:	**Recovery in adult patients hospitalised with community-acquired pneumonia - an exploratory study**
REC reference:	**18/WM/0117**
Protocol number:	**1.0**
IRAS project ID:	**242481**

Thank you for your letter of 30/04/2018. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 23 April 2018

Documents received

The documents received were as follows:

Document	*Version*	*Date*
IRAS Application Form [IRAS_Form_30042018]		30 April 2018
Letters of invitation to participant [Participant Information Sheet v1.1]	1.1	25 April 2018
Participant information sheet (PIS) [CAP Recovery Protocol v1.1]	1.1	25 April 2018

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	*Version*	*Date*
GP/consultant information sheets or letters [GP Letter]	1.0	19 March 2018
Interview schedules or topic guides for participants [Participant Schedule]	1.0	19 March 2018
IRAS Application Form [IRAS_Form_29032018]		29 March 2018
IRAS Application Form [IRAS_Form_30042018]		30 April 2018
Letter from funder [Nottingham Hospitals Charity Letter]	1.0	15 February 2018
Letters of invitation to participant [Participant Information Sheet v1.1]	1.1	25 April 2018
Participant consent form [Participant Consent Form]	1.0	19 March 2018
Participant information sheet (PIS) [CAP Recovery Protocol v1.1]	1.1	25 April 2018
Referee's report or other scientific critique report [Peer Review Form / Scientific Critique]	1.0	15 February 2018
Research protocol or project proposal [CAP Recovery Protocol v1.0]	1.0	19 March 2018
Summary CV for Chief Investigator (CI) [WSL_CV]	1.0	15 February 2018
Summary CV for student [HP_CV]	1.0	15 February 2018
Summary CV for supervisor (student research) [WSL_CV]	1.0	15 February 2018
Summary CV for supervisor (student research) [TM_CV]	1.0	15 February 2018
Summary CV for supervisor (student research) [CB_CV]	1.0	15 February 2018
Validated questionnaire [MoCA Test Version 1]	1.0	08 March 2018
Validated questionnaire [MoCA Test Version 2]	1.0	08 March 2018
Validated questionnaire [MoCA Test Version 3]	1.0	08 March 2018
Validated questionnaire [Fatigue Assessment Scale]	1.0	08 March 2018
Validated questionnaire [MFI]	1.0	08 March 2018
Validated questionnaire [CAP-Symptom score]	1.0	08 March 2018
Validated questionnaire [MRC Dyspnoea Scale]	1.0	08 March 2018

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

18/WM/0117	Please quote this number on all correspondence

Yours sincerely

George R. Martin
REC Manager

E-mail: NRESCommittee.WestMidlands-Solihull@nhs.net

Copy to: Dr Harry Pick
Natalie McGregor, Nottingham University Hospitals NHS Trust

d) Inspiratory Muscle Training (IMT) for adults discharged from hospital with community-acquired pneumonia (CAP) – a feasibility study;

NHS
Health Research Authority

Dr Wei Shen Lim
Nottingham City Hospita
Hucknall Road
Nottingham
NG5 1PB

Email: hracpprovals@nhs.net

24 February 2017

Dear Dr Lim

Letter of HRA Approval

Study title:	**Inspiratory muscle training for adults discharged from hospital with community acquired pneumonia – a pilot study**
IRAS project ID:	**204371**
REC reference:	**17/EE/0043**
Sponsor	**Nottingham University Hospitals R&D**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
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- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details

and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

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- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

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- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-bsc-rg-review.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please email the HRA at hra.approval@nhs.net. Additionally, one of our staff would be happy to call and discuss your experience of HRA Approval.

IRAS project ID	204371

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **204371**. Please quote this on all correspondence.

Yours sincerely

Beverley Mashegede
Assessor

Email: hra.approval@nhs.net

Copy to: Dr Tom Bewick, Sponsor Contact

Dr Natalie McGregor, Lead NHS R&D Contact

Appendix A - List of Documents

The final document set assessed and approved by HRA Approval is listed below.

Document	Version	Date
Contract/Study Agreement [mNCA]		
Contract/Study Agreement [Statement of Activities]		22 February 2017
GP/consultant information sheets or letters [GP letter]	1.0	06 January 2017
Instructions for use of medical device [Brochure for powerbreathe device]	n/a	06 January 2017
IRAS Application Form [IRAS_Form_17012017]		17 January 2017
IRAS Application Form XML file [IRAS_Form_17012017]		17 January 2017
IRAS Checklist XML [Checklist_08022017]		08 February 2017
Non-validated questionnaire [telephone questionnaire]	1.0	06 January 2017
Other [Schedule of Events]		22 February 2017
Participant consent form [consent form]	1.0	06 January 2017
Participant information sheet (PIS)	1.2	24 February 2017
Referee's report or other scientific critique report [Peer review]	n/a	26 September 2016
Research protocol or project proposal [Protocol]	1.0	06 January 2017
Summary CV for Chief Investigator (CI) [CV_CI]	n/a	10 January 2017

Appendix 4; Questionnaires

a) CAP symptom core

CAP-Symptom Score

- **Introduction to CAP-Symptom Questionnaire to be read to the patient.**

Patients with pneumonia sometimes experience symptoms or problems which we are evaluating as part of the study in which you are currently participating. We would therefore like to ask you a few questions about your own current experience in that respect. I am going to read you a list of symptoms or problems. For each of them, I will ask you the extent to which the symptom/problem has bothered you in the past 24 hours: not at all, a little, moderately, quite a bit, or extremely. If you have not had the symptom / problem in the past 24 hours, please let me know.

Overall, the interview will only take a few minutes and the questions are simple to answer. Please remember that you should answer about what has happened in the past 24 hours.

In the past 24 hours, how much have you been bothered by;						
Symptom	Patient did not have symptom / problem	Patient had symptom/problem and it bothered them;				
1. Coughing		Not at all	A little	Moderately	Quite a bit	Extremely
2. Coughing up phlegm / sputum	0	1	2	3	4	5
3. Coughing up blood	0	1	2	3	4	5
4. Chest pain	0	1	2	3	4	5
5. Shortness of breath	0	1	2	3	4	5
6. Sweating	0	1	2	3	4	5
7. Chills	0	1	2	3	4	5
8. Headache	0	1	2	3	4	5
9. Nausea	0	1	2	3	4	5
10. Vomiting	0	1	2	3	4	5
11. Diarrhoea	0	1	2	3	4	5
12. Stomach pain	0	1	2	3	4	5
13. Muscle pain	0	1	2	3	4	5
14. Lack of appetite	0	1	2	3	4	5
15. Trouble concentrating	0	1	2	3	4	5
16. Trouble thinking	0	1	2	3	4	5
17. Trouble sleeping	0	1	2	3	4	5
18. Fatigue	0	1	2	3	4	5

b) MFIS

Modified Fatigue Impact Scale (MFIS)

Fatigue is a feeling of physical tiredness and lack of energy that many people experience from time to time. But people who have medical conditions like MS experience stronger feelings of fatigue more often and with greater impact than others.

Following is a list of statements that describe the effects of fatigue. Please read each statement carefully, the circle the one number that best indicates how often fatigue has affected you in this way during the past 4 weeks. (If you need help in marking your responses, tell the interviewer the number of the best response.) Please answer every question. If you are not sure which answer to select choose the one answer that comes closest to describing you. Ask the interviewer to explain any words or phrases that you do not understand.

Because of my fatigue during the past 4 weeks

		Never	Rarely	Sometimes	Often	Almost Always
1.	I have been less alert.	0	1	2	3	4
2.	I have had difficulty paying attention for long periods of time.	0	1	2	3	4
3.	I have been unable to think clearly.	0	1	2	3	4
4.	I have been clumsy and uncoordinated.	0	1	2	3	4
5.	I have been forgetful.	0	1	2	3	4
6.	I have had to pace myself in my physical activities.	0	1	2	3	4
7.	I have been less motivated to do anything that requires physical effort.	0	1	2	3	4
8.	I have been less motivated to participate in social activities.	0	1	2	3	4
9.	I have been limited in my ability to do things away from home.	0	1	2	3	4
10.	I have trouble maintaining physical effort for long periods.	0	1	2	3	4
11.	I have had difficulty making decisions.	0	1	2	3	4
12.	I have been less motivated to do anything that requires thinking	0	1	2	3	4
13.	My muscles have felt weak	0	1	2	3	4
14.	I have been physically uncomfortable.	0	1	2	3	4
15.	I have had trouble finishing tasks that require thinking.	0	1	2	3	4
16.	I have had difficulty organizing my thoughts when doing things at home or at work.	0	1	2	3	4
17.	I have been less able to complete tasks that require physical effort.	0	1	2	3	4

		Never	Rarely	Sometimes	Often	Almost Always
18.	My thinking has been slowed down.	0	1	2	3	4
19.	I have had trouble concentrating.	0	1	2	3	4
20.	I have limited my physical activities.	0	1	2	3	4
21.	I have needed to rest more often or for longer periods.	0	1	2	3	4

Instructions for Scoring the MFIS

Items on the MFIS can be aggregated into three subscales (physical, cognitive, and psychosocial), as well as into a total MFIS score. All items are scaled so that higher scores indicate a greater impact of fatigue on a person's activities.

Physical Subscale

This scale can range from 0 to 36. It is computed by adding raw scores on the following items: 4+6+7+10+13+14+17+20+21. 0

Cognitive Subscale

This scale can range from 0 to 40. It is computed by adding raw scores on the following items: 1+2+3+5+11+12+15+16+18+19. 0

Psychosocial Subscale

This scale can range from 0 to 8. It is computed by adding raw scores on the following items: 8+9. 0

Total MFIS Score

The total MFIS score can range from 0 to 84. It is computed by adding scores on the physical, cognitive, and psychosocial subscales. 0

c) FAS

Fatigue Assessment Scale (FAS)

Below are a number of questions about possible complaints. Please circle the answer to each question that is applicable to you. Please give an answer to each question, *even if you do not have any complaints at the moment*. The aim of this questionnaire is to find out how you experience your complaints. There are no correct or incorrect answers. It is important that you are honest.

General information:

Date: __-__-200_

Name: _____

Date of birth: __-__-19__

Sex: male / female

Using prednison: no / yes

Year of diagnosis of sarcoidosis: _____

e-mail address: _____

Information given by the physician:

TTT: normal / disturbed

Disorder: sarcoidosis / diabetes / other: _____

Prednison (corticosteroid) use: no / yes

Methotrexate use: no / yes

Other immunoregulatory drug use: no / yes

email: ildinfo@lung.azm.nl

The following ten statements refer to how you usually feel. Per statement you can choose one out of five answer categories, varying from Never to Always. Please circle the answer to each question that is applicable to you. Please give an answer to each question, *even if you do not have any complaints at the moment*.

1 = Never, 2 = Sometimes; 3 = Regularly; 4 = Often and 5 = Always.

	Never	Sometimes	Regularly	Often	Always
1. I am bothered by fatigue	1	2	3	4	5
2. I get tired very quickly	1	2	3	4	5
3. I don't do much during the day	1	2	3	4	5
4. I have enough energy for everyday life	1	2	3	4	5
5. Physically, I feel exhausted	1	2	3	4	5
6. I have problems to start things	1	2	3	4	5
7. I have problems to think clearly	1	2	3	4	5
8. I feel no desire to do anything	1	2	3	4	5
9. Mentally, I feel exhausted	1	2	3	4	5
10. When I am doing something, I can concentrate quite well	1	2	3	4	5

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