Community Acquired Pneumonia

Variation in Healthcare Outcomes and the Effectiveness of the Pneumococcal Vaccine

Student ID: 4317525
Supervisors: Professor Tricia McKeever and Professor Wei Shen Lim

Hannah Lawrence
Hannah.lawrence1@nottingham.ac.uk; Hannah.lawrence9@nhs.net

Abstract

Introduction

Community acquired pneumonia (CAP) remains a leading cause of emergency hospital admission in the UK. Despite established vaccination programs and effective antimicrobial treatment, it continues to be associated with substantial morbidity, mortality and healthcare costs worldwide. Variation in healthcare is well established but, in relation to outcomes in adults hospitalised with CAP, is incompletely described. Firstly, this thesis describes reasons for mortality and readmission following hospitalisation with CAP in England. Secondly, it investigates variation in healthcare outcomes of adults hospitalised with CAP with reference to variation between institutions, socioeconomic groups and by time of presentation to hospital. Thirdly, it analyses the effectiveness of the 23-valent pneumococcal polysaccharide vaccine (PPV23) in preventing vaccine-type pneumococcal pneumonia in adults.

Methods

Three main data sources are used within this thesis. In brief, data are derived from: i) the British Thoracic Society national CAP audit database, ii) NHS digital's Hospital Episode Statistics dataset, and iii) a longitudinal cohort study of adults hospitalised with CAP within the Greater Nottingham area.

Results

This thesis reports that the most common reason for readmission within 30-days of index CAP admission was pneumonia. Inpatient mortality was high in this group; they were over twice as likely to die during readmission than those readmitted for other reasons. Greater social deprivation was associated with increased 30-day mortality in persons aged <65 years, but not in older adults. Regardless of age, increasing deprivation was associated with increasing risk of hospital readmission. There was no evidence of increased mortality for patients admitted at

the weekend with CAP despite an older cohort with higher severity disease. Analysis of variation in BTS audit data found inter-Trust variation in 30-day mortality and readmission rates were low. Greater variation in length of stay and process of care measures were observed. However, no significant association between outlier status for mortality and variation in process of care measures was observed. In addition, a high proportion of the observed variation in all outcome measures examined could be attributed to chance. Lastly, in the setting of an established national childhood PCV13 vaccination programme, PPV23 vaccination in clinical at-risk patient groups and adults ≥65 years of age appears moderately effective against hospitalisation with PPV23 serotype pneumococcal pneumonia.

Conclusion

This thesis describes a significant ongoing burden of adverse outcomes associated with admission to hospital in the UK with CAP and has clear implications in the context of the recent global COVID-19 pandemic. Areas for further study identified by this thesis include: i) the role of revaccination against pneumococcal disease in adults, ii) the short-term health effects of pneumonia following discharge from hospital, and iii) the development of a platform to identify Trusts with outlying healthcare outcomes using the methodology described in this thesis.

Work arising from this Thesis

Publications to date:

1) "Variation in clinical outcomes and process of care measures in community acquired pneumonia: a systematic review" Lawrence et al. 2020; Pneumonia; DOI 10.1186/s41479-020-00073-4
2) "Admission to hospital in the UK at a weekend does not influence the prognosis of adults with community-acquired pneumonia" Lawrence et al. 2020; Thorax; DOI 10.1136/thoraxjnl-2019-214318
3) "Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against vaccine serotype pneumococcal pneumonia in adults: A case-control test-negative design study" Lawrence et al. 2020; PLoS Med; DOI 10.1371/journal.pmed.1003326

Online Reports:

1) "Variation in healthcare outcomes of adults hospitalised with community acquired pneumonia: BTS National Community Acquired Pneumonia (CAP) Audit analysis (2018/19)" British Thoracic Society Online publication; submitted, expected publication date July 2021.

Conference Presentations

1) "Variation in healthcare outcomes of adults hospitalised with community acquired pneumonia: BTS National CAP audit analysis" British Thoracic Society winter meeting symposium presentation, 17th Feb 2021

Conference Abstracts

1) "Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against vaccine serotype pneumococcal pneumonia in adults" Lawrence et al. ECCMID 2020 conference abstract

Acknowledgments

I would like to thank all participants who gave their consent to be enrolled in the studies contained within this thesis and all clinicians involved in data collection for the national BTS CAP audit. I am very grateful to the staff at the BTS, particularly Sally Welham, Christina Moll and Laura Searle, for their support and collaboration. I am grateful to the members of the Nottingham Pneumonia Patient and Public Involvement group who have provided their time and personal perspectives on all projects in this thesis.

I would like to thank the members of the medical and nursing staff of Nottingham University Hospitals NHS Trust for their support and cooperation with the data collection for the primary study on which the work in Chapter 7 is based. I am grateful to Carmen Sheppard, Seyi Eletu, David Litt and Normal Fry from the Respiratory and Vaccine Preventable Bacteria Reference Unit at Public Health England and to Caroline Trotter from the University of Cambridge for their collaboration with this work. I would particularly like to thank Rochelle Edwards-Pritchard for all her help in the lab at Nottingham.

I am indebted to our research team at Nottingham, particularly Drs Harry Pick, Vadsala Baskaran and Debbie Ashton, for their help bouncing ideas around, support and humour throughout. I am very grateful to all my friends, particularly Drs Ireti Adejumo, Priya Daniel, Emma O'Dowd and Karmel Webb for providing much needed motivation when required.

This thesis would not have been possible without the consistent guidance from my supervisors, Professor Tricia McKeever and Professor Wei Shen Lim. I am very thankful for all their time and efforts that continued despite the somewhat distracting global COVID-19 pandemic.

Finally, I would like to thank my family and my other half, Delme Luff, for putting up with me and allowing me the time to complete this thesis.

Table of Contents

Table of Tables

Table of Figures

Chapter 1 - Introduction

Community acquired pneumonia (CAP) in hospitalised individuals is defined by the British Thoracic Society (BTS) as a disease with "symptoms and signs consistent with an acute lower respiratory tract infection associated with new radiographic shadowing for which there is no other explanation" (1). The first section of this chapter discusses the health burden, aetiology and outcomes associated with CAP. The second section introduces variation in healthcare. The third section introduces *Streptococcus pneumoniae*, the most common bacterial cause of CAP, and the vaccines currently in use in the United Kingdom (UK).

1.1 Community Acquired Pneumonia

1.1.1 Burden of Disease

1.1.1.1 Incidence

CAP is a very common disease however estimated incidence varies markedly according to disease definition used (clinical radiographic diagnosis or ICD10 diagnostic codes), setting examined (hospital vs community cases) and geographical area (2). It follows a "U-shaped" distribution, being most common at the extremes of age; in childhood when the immune system is developing and in older age due the effect of immunosenescence and related co-morbidities (3-6).

In 2012, the British Lung Foundation used a GP database to estimate the annual incidence of pneumonia to be 345 people for every 100 000 people in the UK (7). Millet et al. used GP practice data linked with Hospital Episode Statistic (HES) data and found the incidence of all cause pneumonia in UK adults ≥65 years in the community to be 7.99/1000 person years, with rates increasing with age and social deprivation (3). In Europe, a review by Torres et al. estimated the incidence of all cause pneumonia at between 68-7000 cases per 100 000 population, however estimates varied greatly by country, age

group, study and time period (2). Prospective cohort studies in the US have estimated the annual incidence of hospitalised CAP as 634 per 100 000 adults, equating to a burden of over 1.5 million adults per year across the country (8).

1.1.1.2 Morbidity and mortality

CAP remains the leading infectious cause of death globally with the highest mortality seen at those in the extremes of age (9). In the UK in 2012, pneumonia (community and hospital acquired) was the third leading cause of death from respiratory disease behind lung cancer and COPD with the majority of deaths occurring in those aged 65 or above (7). The global burden of diseases study estimated lower respiratory tract infections as the fourth highest value of years of life lost, behind ischaemic heart disease, neonatal disorders and stroke (9). Pneumonia (community and hospital acquired) is the sixth biggest cause of death in the UK (10).

1.1.1.3 Economic burden

Pneumonia is associated with significant economic burden. In Europe, it is estimated that the direct costs of pneumonia amount to 2.5 billion Euros per annum with the majority of this cost comprised of inpatient care (11). This is particularly significant as the age-standardised incidence of hospitalisation with CAP in England is increasing (12). In the US, it is estimated that the direct costs of pneumonia amount to 13.4 billion USD per annum, again with the highest costs from inpatient care (13).

1.1.2 Aetiology of CAP

The microbiology of CAP varies geographically, over time and with the population studied (1). The most common bacterial cause identified in both inpatients and outpatients with CAP worldwide is *Streptococcus*

Pneumoniae, identified in 33-50% of cases with an aetiological diagnosis (14). Other common causative organisms include *Haemophilus influenzae*, *Staphylococcus aureus*, *Klebsiella* and viruses including Influenza (15). Diagnostic techniques used to identify the causative pathogen include microbiological culture (blood, sputum, pleural fluid, broncho-alveolar lavage fluid), immunoassays (urine, serum, sputum) and polymerase chain reaction (PCR) techniques to identify both bacteria and viruses. Despite improved diagnostic techniques, no pathogen is identified in between 35 – 68% of cases (15). Identification of a causative organism depends on the completeness and timing of sampling and the specificity and sensitivity of the microbiological tests used.

1.1.2 Outcomes associated with CAP

1.1.2.1 Mortality

Estimated mortality from CAP depends on the population studied, setting and the causative pathogen. The age-standardised mortality rate for pneumonia varies internationally with estimates suggesting the UK has the third highest mortality rate in Europe (10). In the UK, the mortality of patients hospitalised with CAP has decreased since the introduction of the current BTS and NICE guidelines in 2009 and 2014 from 20.2% in 2009 to 10.4% in 2019 (16-18).

1.1.2.2 Length of Hospital Stay

Community acquired pneumonia is a leading cause of hospital admission in the UK and worldwide (7, 19). The median length of stay (LOS) in those surviving to discharge in the UK is 5 days (IQR 2-8) (17). Inpatient admission is responsible for an estimated 87% of healthcare costs in patients with CAP in the UK (20). Decreasing the LOS in CAP where appropriate was a target of the NHS England and NHS Improvement Same Day Emergency Care CQUIN in 2019 (21).

1.1.2.3 Readmission

In the UK, the proportion of patients readmitted within thirty-days of discharge following their index admission with CAP has increased over the past 10 years, now occurring in 14-16% of those surviving to discharge (17, 22). Causes of readmission are not well understood. International studies estimate that 25-37.5% of readmissions are related to the index pneumonia admission, whilst the remainder are unrelated (23-25). Identified risk factors for readmission include demographic factors (increasing age, socio-economic factors), co-morbidity, disease factors (severity, decompensation of co-morbidity during admission) and prior healthcare utilisation (23-27). *Jang et al.* found risk factors for pneumonia related and unrelated readmissions were different (24).

1.1.2.4 Critical Care use

Existing evidence supports early intervention and consideration of ICU in appropriate patients with severe CAP (1, 28). From BTS audit data, the proportion of patients hospitalised with pneumonia admitted to critical care in the UK is 5% (17). Critical care admission rates in the USA are higher at 15-22% of hospitalised patients (29-31). This likely reflects highly variable ICU admission criteria across differing healthcare systems (32). Risk factors for developing severe CAP requiring critical care admission include advancing age, co-morbid illness (particularly chronic respiratory, cardiovascular disease and diabetes mellitus), cigarette smoking, alcohol abuse and immune suppression (33).

1.1.3 Process of care measures in CAP

Process of care (POC) measures are interventions or treatments considered key in the gold standard management of a patient hospitalised with CAP according to international medical society guidelines (1, 18, 34, 35). They are commonly used as targets in guidelines and national audits (17).

1.1.3.1 Severity Scoring

Several scoring systems to predict the severity of disease in patients with CAP are in use internationally. In the UK, the prognostic score recommended for use by national guidelines is the CURB-65 score (1, 36). This attributes one point for each of the following features present: **C**onfusion, **U**rea > 7 mmol/l, **R**espiratory rate ≥ 30/minute, systolic **B**lood pressure <90mmHg or diastolic blood pressure ≤ 60mmHg and Age ≥ **65** years. A score of 0-1, 2 and ≥3 denote low, intermediate and high severity disease with associated increases in mortality across the groups (1.5%, 9.2% and 22% in low, intermediate and high severity disease respectively). It has been validated in large national and international cohorts (28, 37). Use of scoring systems differs internationally with the American Thoracic Society guidelines recommending the use of the Pneumonia Severity Index (PSI) (35).In addition to the domains in the CURB-65 score, the PSI includes sex, co-morbidities, biochemical and radiology results. No significant difference between the scores for predicting mortality in patients hospitalised with CAP has been observed (38).

1.1.3.2 Antimicrobial therapy

Antimicrobial therapy against CAP in the UK is usually decided by local antimicrobial guidelines and based on national guidance and local resistance patterns. The National Institute for Clinical Excellence (NICE) recommends antimicrobial prescribing based on location and severity score (1) (36). Delay in time between admission and receipt of antibiotics is associated with greater 30-day inpatient mortality (39).

1.1.3.3 Imaging in CAP

In order to obtain a timely radiological diagnosis of CAP, a chest radiograph within four hours of admission is recommended by national guidelines (1, 18). Repeat imaging is advised where there has been

failure to improve, a complicated infection or an alternate diagnosis is suspected. It is recognised that when compared against CT chest findings, the CXR may be both ‘falsely negative’ and ‘falsely positive’ in a proportion of cases (40). In a French study of adults admitted via the Emergency Department (ED) with suspected CAP but excluding those with high severity illness (CRB65 score ≥3), of 319 adults studied, 188 (59%) had CXR features of pneumonia. Of those with a “negative” CXR, 30% had an infiltrate on CT. In a Swiss study of patients aged >65 years admitted with suspected CAP (n=200), 113 (57%) had a high probability of CAP based on initial CXR and clinical findings. Of those with initial intermediate and low probabilities of CAP (n=87), 30% were considered to have a high probability of CAP following review of CT chest findings (40, 41). Whether clinical differences exist between CXR proven and CT only proven pneumonia is not clear. A multicentre prospective study in the US reported on 2251 adults with CAP of which 3% had pneumonia visualised on CT scan but not concurrent CXR (42). The pathogens, disease severity and outcomes were similar in both groups.

Lung ultrasonography has an established role in the diagnosis of complications of pneumonia, particularly parapneumonic effusion. Increasingly, it is used in the diagnosis of pneumonia itself, however the sensitivity and specificity of the test remain variable and operator dependent (43).

1.2 Variation in Healthcare

1.2.1 Definition - Warranted vs Unwarranted

The concept of variation in health care is divided into two distinct classifications: “warranted” and “unwarranted”. Warranted variation reflects differences due to patient-centred care, requirements of the population served or innovation during adoption of novel treatments (44). This type of variation is considered acceptable and even desirable. In contrast, unwarranted variation in healthcare is considered potentially harmful for patient care. John Wennberg described unwarranted variation as “variation that cannot be explained on the basis of illness, medical evidence or patient preference” (45). It can lead to: i) underuse of high-value interventions by certain populations creating inequitable health care, and ii) overuse of lower value interventions and putting strain on increasingly stretched resources.

Variation in health care is long established within health care research. In 1938, Glover described marked variation between geographical areas in the incidence of tonsillectomy in elementary school children in the UK that showed no apparent association with “personal factors” (eg. overcrowding, unemployment or provision of dental care) that may contribute to chronic tonsillitis (46). Following on from Glover’s work, health care variation has been described internationally and is considered ubiquitous across health care conditions. In the USA, the Dartmouth Atlas Project using Medicare data has documented variations in health care across the country for over twenty years (47). Adapting this idea, countries in Europe and Australasia have produced Atlases of Variation focussing on different aspects of healthcare and covering a wide set of medical conditions (48-52). Consequently, there is consistent published international evidence documenting clinical variation in various health care systems. Despite several decades of published evidence however, unwarranted variation persists in health care and directly impacts on equity services and health outcomes (53). Recent studies reveal a seven-fold variation in tonsillectomy rates across local authority areas in England and unwarranted variation in

same day discharge rates persist, suggesting that despite awareness the causes of health care variation have not been tackled in full (54, 55).

1.2.2 Evidence for variation in CAP

There is international variation in the age-standardised mortality rates for pneumonia by country (10). Additionally, some evidence from national atlases for variation in the outcomes of patients hospitalised with CAP exists. The NHS RightCare 2nd Atlas of variation in risk factors and healthcare for respiratory disease in England (2019) used routinely collected NHS data to display variation in outcome measures across common respiratory diseases (56). It examined three main outcomes in pneumonia across geographical units; median LOS, the proportion of 0-1 days admissions (a proxy for potentially ambulatory admissions) and mortality rate from pneumonia. It reported geographical variation between CCGs for all three outcomes. The mortality rate differed by 2.8 fold (29.5-83.2 per 100 000 population) whilst a 3.5-fold difference in median LOS (2-7 days) and proportion of 0-1 day admissions (11.1-38.5%) was observed (56). The atlases show the magnitude of variation in mortality to be persistent since the first atlas in 2009, despite a national trend for decreasing overall inpatient mortality from CAP in this time-period (16, 17).

1.2.3 Potential causes of unwarranted variation

The Dartmouth Atlas Project proposed three categories of care to provide a framework for examining the causes of unwarranted variation and directing efforts to target it: i) Effective care, ii) preference-sensitive care, and iii) supply-sensitive care (45). Effective care includes treatments, interventions or services with strong published evidence bases that are generally agreed to be better than any alternative treatment option. This care reflects (current) gold standard care and

should be achieved in all eligible patients. Unwarranted variation here is due to underuse of an effective care in eligible patients.

Preference-sensitive care is where more than one option is available and the choice is dependent on patient preference or physician behaviour. Uncertainty might exist for this type of care due to a lack of scientific basis to support one option over others. Warranted variation in preference-sensitive care may reflect true patient-centred care arising from shared decision making. However, unwarranted variation arises from preference-sensitive care often due to physician opinion and behaviour (45).

Supply-sensitive care reflects services where the supply of a resource effects utilisation rates. Physician decisions regarding supply sensitive care are strongly influenced by capacity of available resources e.g. ICU beds (45).

In the treatment of CAP, established guidelines on the management of CAP recommend interventions based on currently available evidence as detailed in section 1.1.3 (1, 18, 35, 36, 57). In the UK, national guidelines are interpreted by local hospital trusts in the context of their local population and resources, forming local treatment pathways and guidelines. In practice, these guidelines are further interpreted by individual clinicians and applied to individual patients. Some aspects of care for patients with CAP, for example the timely administration of appropriate antibiotic therapy or the delivery of oxygen to an acutely hypoxic patient, constitute effective care. Other interventions (antimicrobial testing for specific pathogens, post discharge follow up arrangements, duration of antibiotic course) are subject to local variations in practice and consequently represent either preference or supply sensitive care.

1.3 Pneumococcal Pneumonia

Pneumococcal pneumonia remains the most common bacterial cause of pneumonia identified worldwide (14, 15). Despite a worldwide decrease in childhood mortality from pneumococcal pneumonia between 1990-2017, among adults over 70 deaths have increased by 60.4% (95% CI 39.7-79.9%) (58).

1.3.1 History of Streptococcus Pneumoniae

S. Pneumoniae was first discovered in 1881 independently by Pasteur in France and Sternberg in the New Orleans, USA (59, 60). In 1886, Weichelbaum established the predominant role of S. Pneumoniae as a causative pathogen in lobar pneumonia (59, 61). By 1894, *S. Pneumoniae* was recognised as the causative organism of epidemic outbreaks of pneumonia and sinusitis in gold miners in Johannesburg, South Africa. With an estimated attack rate of 100 per 1000 persons per year and case fatality of 25%, the disease burden threatened the existence of the gold mining industry (62). Subsequently, the first major attempts to control pneumococcal infection through both vaccination and the development of antimicrobial agents commenced in the early 1900s (62).

1.3.2 Pneumococcal capsule – serotypes

The main virulence factor of *S. Pneumoniae* is the pneumococcal capsule containing capsular polysaccharides (63). The capsule's primary role is as a physical barrier to shield the cell wall from host antibodies and complement, thus evading opsonisation via the innate immunity. The role of the capsule was first recognised in the 1930s when serologic heterogeneity was observed among convalescent phase serum (64). This led to the recognition of serotypes and discovery that immune protection against *S. Pneumoniae* is primarily serotype specific. A serotype is a *S. Pneumoniae* strain producing a

capsular polysaccharide with a unique chemical structure and immune properties. A serogroup includes serotypes that share serologic properties; they cross react to specific antibodies against other group members. To date, there are 97 known serotypes within 46 serogroups identified (65). Cell wall polysaccharide (CWP) is covalently linked to capsular polysaccharide via peptidoglycan; its structure is largely invariant across serotypes. Serotypes differ in their ability to elicit a host immune response (via antibodies or complement), invasiveness profile and disease characteristics (63, 65).

1.3.3 Pneumococcal Vaccination types

Two types of pneumococcal vaccination currently available with different mechanisms of action: i) the 23 valent pneumococcal polysaccharide vaccination (PPV23) and ii) the Pneumococcal conjugate vaccines (PCV) (66). Both vaccine types are inactivated vaccines. The polysaccharide vaccine contains purified capsular polysaccharide antigens that stimulate B cells in the marginal zone to produce serotype specific antibodies in a T cell independent manner (67). The addition of a carrier protein to the polysaccharide antigen produces a conjugate vaccine. PCVs stimulate the immune system to produce antibodies via a T cell dependent process. In contrast to the T cell independent mechanism of PPV23, the T cell dependent mechanism of PCVs induces long term immunological memory (67, 68). From immunogenicity studies, the duration of protection afforded by PPV23 is estimated at between 3-10 years (69).

1.3.3.1 Pneumococcal Conjugate Vaccines

In the UK, PCV vaccination was first available for children in at risk groups under the age of two years in 2002 (66). In 2006, PCV7 (containing serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) was included in the childhood vaccination programme; it achieved very high vaccine coverage (>90%). PCV7 was replaced by PCV13 in 2010, providing

protection against 6 additional serotypes (1, 3, 5, 6A, 7F, 19A). The current vaccine schedule includes three doses given at 8 weeks, 16 weeks and around 12 months of age (66).

1.3.3.2 Pneumococcal Polysaccharide Vaccine

The PPV23 has been available in the UK since the 1980s. In 2003, it was recommended for individuals ≥65 years or those in a clinical risk group as defined by the Public Health England (PHE) Vaccination booklet ("the Green Book") (66). Vaccine coverage in individuals ≥65 years old is currently over 70% (70). In addition to the serotypes covered by PCV13 (with the exception of 6A), it provides protection against a further 11 serotypes (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F).

1.4 British Thoracic Society CAP Audit

One of the primary data sources for the analyses in this thesis is the British Thoracic Society (BTS) National Adult CAP audit. The BTS is a UK charity organisation dedicated to working with healthcare professionals to improve the care of patients with lung diseases. The national BTS adult CAP audit first took place over winter 2009/10 (1st December 2009 – 31st January 2010), following the release of the BTS national guidelines in 2009.(1) The aim was to compare key elements of the management of patient's hospitalised with CAP against guideline standard care. Since then, the audit has run over a further five winters (2010/11, 2011/12, 2012/13, 2014/15 and 2018/19) with increasing participation over each audit cycle.

In the latest audit, 154 participating institutions across the UK submitted 10196 cases of clinical and radiographically confirmed pneumonia. The inclusion and exclusion criteria have remained the same allowing comparability across audit cycles. Participating institutions identify cases retrospectively via ICD10 primary discharge codes mapping to a diagnosis of pneumonia (J12 to J18 inclusive). Each identified case is then screened against the inclusion criteria, namely adults >16 years of age with an acute onset of symptoms and signs of a lower respiratory tract infection with new infiltrates on a chest radiograph performed within 24 hours of admission. Exclusion criteria are: hospital admission within 10 days prior to the index admission, immunocompromise, aspiration pneumonia and transfer from another hospital.

The main strengths of the BTS dataset are that it is a large, robust database of clinician confirmed cases of CAP admitted to hospitals across the UK. Other large databases of patients with pneumonia rely on ICD-10 codes for case finding, however this method has limitations as there is no single diagnostic ICD-10 code to denote CAP. The accuracy of an ICD-10 coded diagnosis of CAP is moderate at 54.1%; the most common reason for a coded case not meeting the audit definition of CAP is a lack of CXR changes consistent with the

diagnosis (17). Studies reliant on data derived from coding alone are therefore at risk of misclassification bias (71). In contrast, the BTS audit requires clinician review of each case prior to its inclusion, ensuring a clearly defined population are included.

Participation in the national audit is open to all Trusts or health boards providing acute hospital care in the UK (approximately 135 acute Trusts in England, 14 health boards in Scotland and 7 in Wales). Active involvement in audit is incentivised by NHS England and engagement with the audit is excellent, particularly in England. Sampling bias introduced by non-participation of poorly performing Trusts cannot be completely excluded. As data are largely derived from England and due to differing health systems internationally, results may be less applicable to devolved nations and other countries.

A further limitation of the audit is that it is time limited to a two-month data collection window. This is primarily because it relies on clinician data entry which is time consuming for local teams and precludes continuous data collection. The chosen two-month winter period (December / January) coincides with predicted peaks in common seasonal respiratory tract pathogens. This may introduce bias towards better care as clinicians are more attuned to a diagnosis of CAP during these months. However, delivery of care may be negatively impacted by the added pressures on the health service at this time caused by increased admissions. Overall, the direction of the bias is complex and difficult to predict. The two-month period remains the same across all audit cycles to facilitate comparison of performance across time.

1.5 Aims of the Thesis

The main aims of this Thesis are:

1) To review current literature on variation in healthcare outcomes of patients hospitalised with CAP.
2) To describe the reasons for i) mortality and ii) readmission in the BTS CAP cohort.
3) To describe the variation between NHS Trusts in healthcare outcomes of adults hospitalised with CAP across England after adjustment for case-mix and accounting for natural variation.
4) To examine the association between mortality following hospitalisation for pneumonia and socioeconomic deprivation.
5) To examine variation in outcomes of patients admitted with CAP to UK hospitals at a weekend compared to a weekday.
6) To analyse the effectiveness of the PPV23 vaccine in preventing vaccine-type pneumococcal pneumonia in adults, using data from the SCAPA study.

Chapter 2 - Variation in clinical outcomes and process of care measures in Community Acquired Pneumonia: a systematic review

2.1 Introduction

Geographical variation in clinical care is considered ubiquitous across all aspects of healthcare. A proportion of variation in healthcare measures is warranted, reflecting true differences in individual healthcare preferences and the needs of the local population served. Conversely, persistent unwarranted variation in clinical care directly impacts on equity of services, population outcomes and use of resources (53). Equitable care across geographical regions has been highlighted as a key concern from a patient viewpoint (49). Inevitably, outcome measures are increasingly used to rank healthcare between regions and hospital providers (72). However, there is concern that such ranking does not account for natural variation between units and may not be reflective of true variation in quality of healthcare (73).

Inter-hospital variation in outcomes of patients hospitalised with CAP was first suggested from retrospective claims-based studies in the USA (74). More recent evidence from large GP databases in the UK have shown that mortality for patients under the age of 75 varies up to nine-fold depending on the geographical location (49). Little is known about the causes of this apparent geographical variation, whether it extends to other outcomes or process of care measures and to what extent it is unwarranted.

The aim of this systematic review was to collate available evidence on regional and inter-hospital variation in the clinical outcomes and

process of care measures of patients hospitalised with CAP and assess the strength of this evidence. Where possible, we also sought to identify any potential causes for any observed variation.

2.2 Methods

Online databases were systematically searched (MEDLINE, EMBASE, Web of Science) using Medical Subject heading (MeSH) terms to identify published and unpublished studies that compared the process of care measures and outcomes of adults hospitalised with CAP between two or more hospitals or geographical regions. As MeSH terms to identify variation excessively limited our search, we also broadened the search strategy to capture all studies on adults hospitalised with community-acquired pneumonia for title screening (Appendix 10.1). Databases were searched from inception to February 2018 inclusive. Title, abstract and full text screening were performed in a three-step process by two independent reviewers (HL, TM) using the online platform Covidence ©. Disagreements were resolved by discussion and involvement of a third reviewer (WSL). Hand searching of references from the list of eligible studies for further references not identified in the initial search was performed. Data extraction was performed by each reviewer (HL, TM) independently using a standardised form. The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (75) and prospectively registered on PROSPERO (CRD42019124068).

All prospective and retrospective observational or randomised controlled studies in any language with no date restriction on publication were considered for inclusion. Studies were included if they enrolled adults (>16 years old) hospitalised with CAP and reported a measure of variation between two or more hospitals or geographically distinct areas

in chosen outcome or process of care measures. For the purpose of this review, included studies defined CAP either; a) clinically as the acute onset of symptoms suggestive of lower respiratory tract infection with new infiltrates on thoracic imaging consistent with pneumonia or b) using recognised International Classification of Disease (ICD) codes pertaining to pneumonia from administrative databases. Geographical units for comparison were defined as geographical regions or geographically separated hospitals serving distinct patient populations. Measures of inter-hospital variability included appropriate descriptive statistics, variance analysis and graphical methods for comparing institutional performance.

Studies were excluded if: 1) they enrolled solely immunosuppressed patients with Human Immunodeficiency Virus (HIV) and Pneumocystis Pneumonia (PCP) 2) they enrolled patients exclusively from a primary care setting or 3) they examined temporal variation in CAP care only. Finally, studies that described or measured implementation of a change from usual care within a hospital setting, for example implementation of a pneumonia care pathway or an alternative antimicrobial regime, were also excluded.

Primary outcome measures of interest were case mortality, length of hospital stay and hospital re-admission rates. In accordance with recognised guidelines for the management of CAP, process of care measures of interest were: a) use of guideline adherent antibiotics; b) admission rates to intensive care units; c) duration of antibiotic treatment (both intravenous and total); d) time to first antibiotic and e) obtaining admission blood cultures (76, 77).

2.2.1 Statistical Analysis

Due to differences in the statistical methods used to evaluate variation across the included studies, a pooled meta-analysis was not possible. Instead, a structured synthesis of the studies was performed by collating: 1) inter-hospital ranges for outcome and process of care measures, 2) variance analysis and 3) statistical methods to quantify or control for natural variation between units.

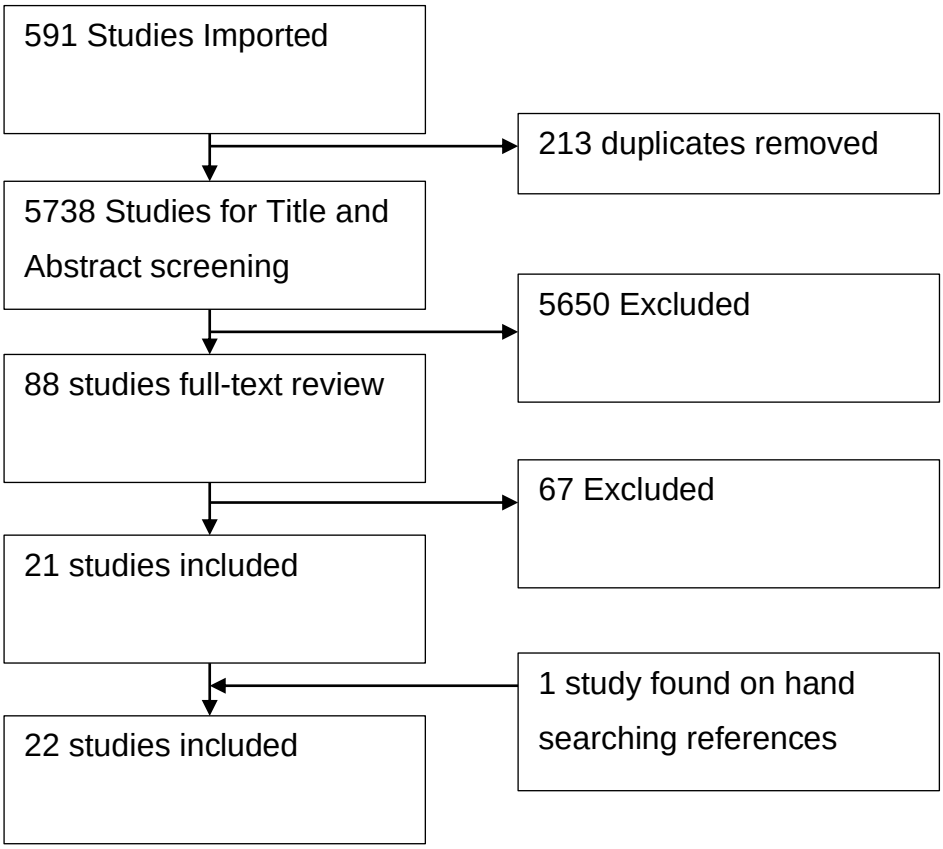
2.2.2 Assessment of Bias

Two reviewers (HL & TM) assessed the methodological quality of studies using a modified quality score based on the Newcastle-Ottawa Scale (Appendix 10.2). This score assesses the risk of bias at outcome level in observational studies in 3 domains: participant selection, comparability of groups and validity of outcome domains. The maximum score on the modified scale used was 10.

2.3 Results

Comprehensive searching identified 5738 papers. Following title and abstract screening, 88 studies were included in the full text assessment, from which 67 studies were excluded; the main reason for exclusion was the lack of reporting on variation (Figure 2.1). One study was identified following hand searching of references and subsequently included in the review (78).

Figure 2.1 - Screening consort diagram



2.3.1 Characteristics of included studies

Twenty-two papers met the inclusion criteria (78-99). Results from two papers were derived from the same study population and were combined for further analysis (94, 96). A further two papers reported results from the same population but different measures, so were both included (87, 93). Details and characteristics of included studies with a description of variation between units compared, their respective populations and disease characteristics are shown in Table 2.1.

Studies differed in design: seventeen were cohort studies (nine retrospective, seven prospective and one mixed), three were analyses of administrative data (79, 91, 99), one was a case control study (89) and one study analysed the baseline population from a randomised control trial (97). The median number of units compared across studies was five (IQR 4-15) with a median of 1022 (IQR 445 – 2009) cases of CAP. Four studies compared geographical regions, the remaining 18

compared hospitals. Retrospective cohort studies compared a greater number of units (range 3-38) than prospective cohort studies; the latter involved a maximum of four units.

The range of quality scores was 5 – 9.5 (mean 6.95, SD 1.45). The three commonest factors missing from the quality score were: no statement accounting for missing data, limited inter-hospital case-mix adjustment for clinical parameters or baseline characteristics and the absence of a financial or affiliation statement. Baseline characteristics of study cohorts were not always comparable. For example, two prospective cohort studies compared study populations with widely different health care resources and baseline characteristics (95, 98). In addition, there were three international studies (80, 81, 98); observed variation in these may reflect differences in international healthcare provision and usage.

Table 2.1 Characteristics of the included studies

Author & Year	Study Design	Country	Number of subunit compared	Total study population	Quality score	POC, Outcome or Both	Variation in Patient population between units	Variation in hospital type / subunit	Variation in disease factors
Subunit of variation: Geographical region or country									
Arnold et al.(80) 2013	Retrospective Cohort	International – 16 countries across USA, Canada, Europe and Latin America	70 hospitals across 3 geographical regions (USA/Canada, Europe, Latin America)	6371	9.5	Both	Significant differences in baseline populations. Latin America lowest prevalence of every co-morbidity.	Variation between hospitals grouped by continents. International variation in healthcare practice and resources.	Europe - fewest low severity scoring patients, greatest number of high severity scoring patients.
Blasi et al.(81) 2013	Retrospective Cohort	International - Europe	10 countries (128 sites)	2039	6.5	Outcome	Not reported	Not reported	Included HCAP in addition to CAP
Lave et al.(91) 1996	Retrospective Analysis of Administrative data	USA	7 geographical regions	36 222	7	Both	Not reported	All hospitals part of a larger non-profit organisation. Bed size varies 80 - 500 beds. Teaching	Not reported

								and non-teaching facilities.	
Remond et al.(95) 2010	Mixed Prospective / Retrospective Cohort	Australia	2 regions (7 hospitals)	293	6.5	Both	Different ethnicity between cohorts	Six small regional hospitals in the Kimberley, one tertiary hospital in Central Australia	Regional differences in isolated causative organisms.
Subunit of variation: Hospital									
Aelvoet et al.(79) 2016	Retrospective Analysis of Administrative data	Belgium	111 hospitals	108 213	7	Outcome	Not reported	All hospitals in Belgium	Not reported
Cabre et al.(82) 2004	Retrospective Cohort	Spain	27 hospitals	1920	6.5	Both	The number of comorbidities varied among hospitals.	All community hospitals - urban and rural	Proportion of patients belonging to each risk class (by PSI) varied widely among hospitals
Capelastegui et al.(83) 2005	Retrospective Cohort	Spain	5 hospitals	1498	6	Both	Statistically significant differences in	All teaching general hospitals	Statistically significant differences

							patient demographic factors between hospitals.	with similar resources	in PSI score classification between hospitals
Dedier et al.(84) 2001	Retrospective Cohort	USA	38 hospitals	1062	5	Both	Not reported	All academic hospitals	Not reported
Feagan et al.(85) 2000	Retrospective Cohort	Canada	20 hospitals	858	6.5	Both	Only comparison reported between teaching and general hospital populations	11 teaching hospitals, 9 community hospitals	Not reported
Fine et al.(78) 1993	Prospective Cohort	USA	4 hospitals	552	9.5	Both	Mean number of comorbid conditions per patient varied significantly among hospitals.	2 university hospitals, one veterans hospitals, one community hospital	Disease severity and aetiology similar across hospitals
Garau et al.(86) 2008	Retrospective Cohort	Spain	10 hospitals	3233	8	Outcome	Not reported	All tertiary hospitals	Proportion of patients belonging to each PSI class varied widely across hospitals, as

									did the proportion with an aetiological diagnosis.
Gilbert et al.(87) 1998	Prospective Cohort	USA/Canada	4 hospitals	1328	9.5	Both	Significant differences in mean age, gender, racial distribution and comorbidities among the 4 sites.	Three university teaching hospitals, one community teaching	Statistically significant differences in causative organisms identified and severity of illness.
Hedlund et al.(88) 2002	Retrospective Cohort	Sweden	17 hospitals	982	5	Outcome		Seven university hospitals, 10 county hospitals.	The mean PSI varied between 0.9 and 1.9 at different sites
Iroezindu et al.(89) 2016	Prospective Case control	Nigeria	4 hospitals	400	6	Outcome	Not reported	All tertiary hospitals	Not reported
Klausen et al.(99) 2012	Retrospective Analysis of Administrative data	Denmark	22 hospitals	11322	8.5	Outcome	Not reported	All Danish public health hospitals	Not reported
Laing et al.(90) 2004	Prospective Cohort	New Zealand	2 hospitals	474	7	Both	Similar demographics between the	"Similar institutions"	No significant differences

							two populations except significant differences in ethnicity and rates of COPD.		in disease severity by PSI.
Malone et al.(92) 2001	Retrospective Cohort	USA	5 hospitals	330 (52 severe)	5.5	POC	Not reported	All acute care facilities (Centura)	Not reported
McCormick et al.(93) 1999	Prospective Cohort	USA/Canada	4 hospitals	1188	9	Both	A younger more mixed-race population identified at one site. The proportion admitted from a nursing home varied from 9-16%.	Three university teaching hospitals, one community teaching	Severity of illness and symptom profiles were similar across hospitals. One hospital had fewer "high risk" aetiology.
Menendez et al.(94) 2003	Prospective Cohort	Spain	4 hospitals	425	7	NA	Not reported	Not reported	Not reported
Reyes Calzada et al.(96) 2007	Prospective Cohort	Spain	4 hospitals	425	6	Both	No significant differences in co-morbidity, age and sex. Smoking significantly	One tertiary and 3 district general hospitals	Not reported

							more frequent in two hospitals.		
Schouten et al.(97) 2005	Analysis of baseline population from RCT	Netherlands	8 hospitals	436	6.5	POC	Not reported	Eight medium sized hospitals in the south-east of the Netherlands	Not reported
Sow et al.(98) 1996	Prospective Cohort	France and New Guinea	2 hospitals	333	5	Outcome	Mean age and pre-existing illness rate was significantly lower in Guinea than France.	One hospital in the Republic of Guinea compared to one in France	Similar severity between cohorts (clinical definition not validated severity score)

2.3.2 Variation in Outcome Measures

2.3.2.1 Inpatient Mortality

Fourteen studies reported variation in in-patient mortality (78, 80-84, 86, 88-91, 95, 98, 99). The mean mortality for each study ranged between 1.1 and 22.6%. The magnitude of the observed range in variation for in-patient mortality was between 1% and 18.6% across studies (n=14, mean 8.4%, SD 6.1). Of eleven studies that performed statistical significance testing, five found statistically significant variation (Figure 2.2 and Table 2.2) (80, 82, 86, 91, 99). All 6 studies that did not find statistically significant variation in inpatient mortality compared 5 or fewer units (78, 83, 89, 90, 95, 98). One study adjusted for natural variation between hospitals; *Aelvoet et al.* used the Spiegaelhalter method to produce funnel plots examining variation in standardised mortality ratios (SMRs) across 111 hospitals in Belgium (79). Their primary model identified five institutions as 'possibly better performing', 7 as 'possibly worse performing' and 81 as 'normally performing' with the remaining 18 in an inconclusive 'to be assessed' category, with subsequent sensitivity analysis confirming these findings.

Figure 2.2 - Inter-hospital variation in inpatient and post-discharge mortality

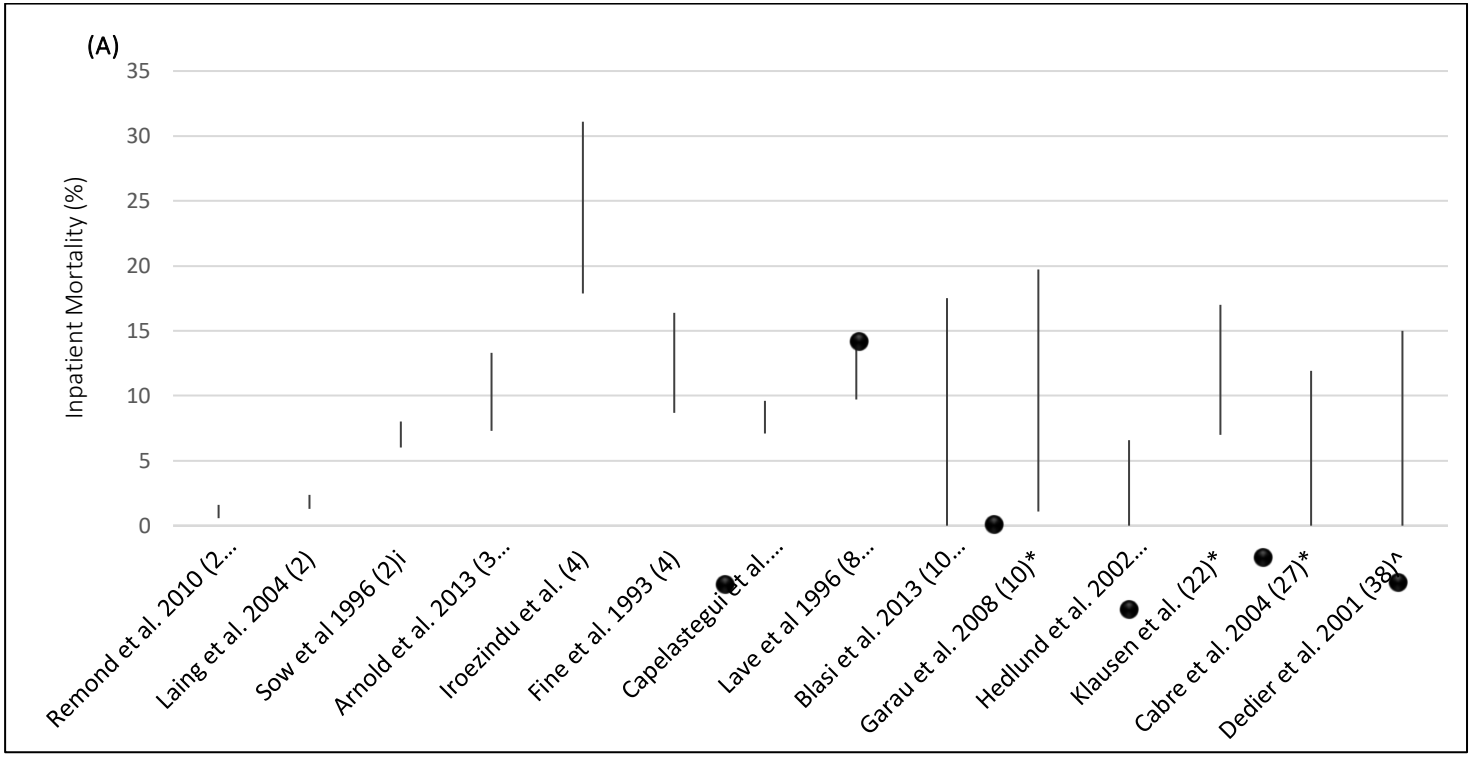
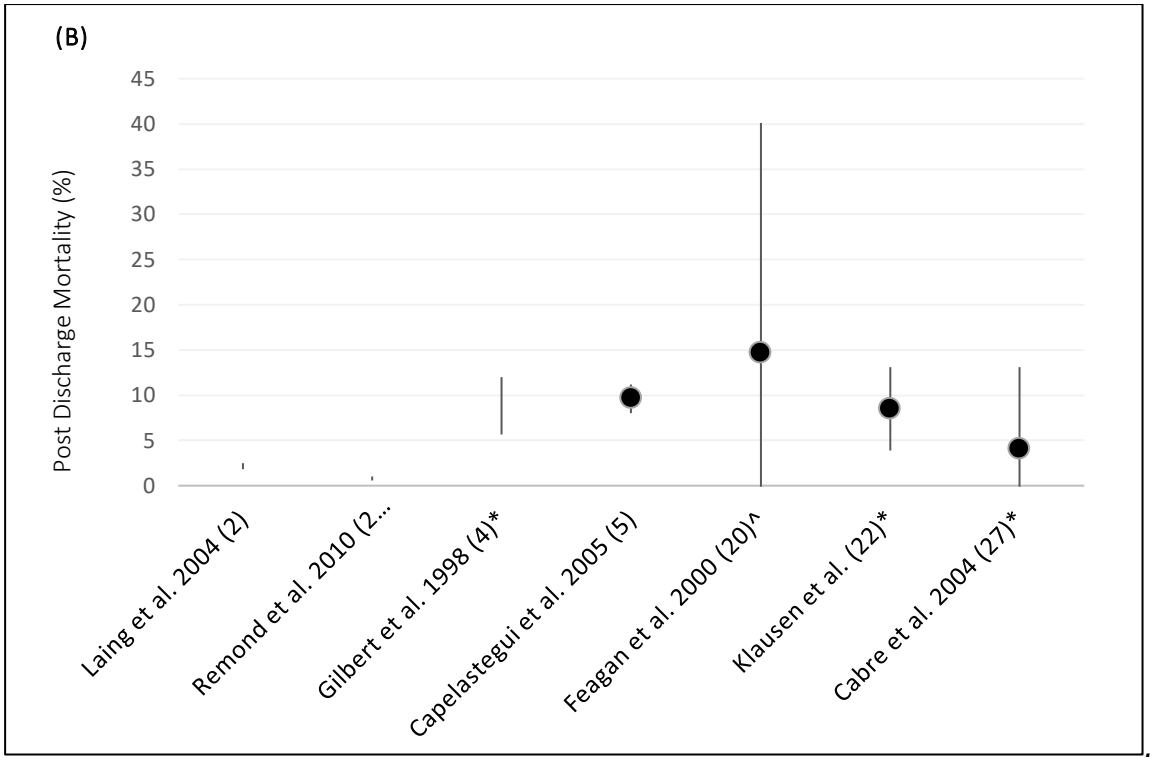


*Figure 2.2: A) Inter-hospital variation in inpatient mortality across studies (%). Range represented as line, dot represents mean value where possible. * denotes a statistically significant result. ^ denotes no reported p value. The letter 'i' represents an international study. The number in brackets represents the number of units compared in the hospitals, unless otherwise stated*



*. B)- Inter-hospital variation in post discharge mortality across studies (%) – 14 days post discharge or 30 days post admission. Range represented as line, dot represents mean value where possible. * denotes a statistically significant result. ^ denotes no reported p value. The number in brackets represents the number of hospitals compared in the study, unless otherwise stated.*

Table 2.2 - Variation in Outcome Measures

Outcome	Study	Number of units	Inter-hospital range of outcome measure (% unless stated otherwise)	P value for difference between units	Mean (SD)	Adjusted?	Comments
Average Length of Stay (days)	*Cabre et al. 2004(82)*	27 hospitals	2.7 – 17.4 (mean days)	0.001	10.0	PSI risk class, discharged to nursing home, admission to ICU	
	Capelasteg ui et al. 2005(83)	5 hospitals	7.3 – 10.6 (mean days)	<0.001	8.6 (1.25)	Adjusted analysis confirmed significant differences in mean LOS of up to 2.9 days (adjusted for PSI score, multi-lobar involvement, COPD and antibiotic treatment prior to admission).	
			6 -10 (median days)	<0.001	IQR 3		
	Dedier et al. 2001(84)	38 hospitals	3 – 8 (median days)	Not reported	Not reported	-	
	Feagan et al. 2000(85)	20 hospitals	5 – 9 (median days)	Not reported	6.83 (1.07)	-	
	Fine et al. 1993(78)	4 hospitals	6.6 – 12.1 (mean days)	<0.05 (Hospital D shorter mean LOS vs Hospitals A,B & C; Hospitals A,C&D	9.28 (2.25)	"Similar trend when adjusted by PSI"	

				each had shorter mean LOS than B)			
	Garau et al. 2008(86)	10 hospitals	7.8 -17.3 (mean days)	< 0.001	11.8 (2.79)	-	
	Hedlund et al. 2002(88)	17 hospitals	4.3 – 8.2 (mean days)	Not reported	Not reported	-	No correlation between mean PSI and mean LOS (p = 0.97)
			4.5 – 7 (median days)	Not reported	Not reported		
	Iroezindu et al.(89)	4 hospitals	Not reported	Not reported	Not reported	-	On multivaritate analysis, predictors of LOS>10 days were care in hospitals A and B (aOR 3.1, 95% CI 1.3-10.5 and aOR 2.2, 95% CI 1.1-11.2 respectively) - adjusted for gender, CURB65, co-morbidity, anaemia, elevated Cr.
	Klausen et al.(99)	22 hospitals	2 – 7 (median days)	Cox adjusted analyses identified 4 hospitals with shorter LOS (p<0.01) and 8 with longer LOS.	5.45 (1.41)	Gender, age, ventilatory support, Chalson index score	
	Laing et al. 2004(90)	2 hospitals	3.0 - 5.9 (mean days)	<0.001	4.45 (2.05)	-	

	Lave et al 1996(91)	8 regions	8.4 – 10.2 (mean days)	<0.1	9.48 (0.53)	-	Differences in LOS across regions remained significant after controlling for severity of illness, aetiology and hospital characteristics (data not presented).
	McCormick et al. 1999(93)	4 hospitals	7.3 – 9.6 (mean days)	<0.001	8.58 (1.03)	PSI risk class, Aetiology, ICU admission in first 24 hours, positive blood culture, discharge to NH, DNAR, employment status	
	Remond et al. 2010(95)	2 geographic regions	4 (median days)	Not reported	Presented as range	Not reported	
	Reyes Calzada et al. 2007(96)	4 hospitals	Not reported	p=0.0001- hospital D median LOS compared to others	NA	-	"Shorter stays were recorded in hospital D, with a median of 6 days p=0.0001"
Inpatient mortality	*Arnold et al. 2013(80)*	3 geographic regions	7.3 – 13.3	<0.0001	9.9% (3.08)	-	
	Blasi et al. 2013(81)	10 countries	0 – 17.5	Not reported	7.9% (6.04)	-	
	Cabre et al. 2004(82)	27 hospitals	0-11.9	0.012 p value for inter hospital difference	4.8%	-	

	Capelastegui et al. 2005(83)	5 hospitals	7.1 – 9.6	0.94	8.62%, (1.01)	-	
	Dedier et al. 2001(84)	38 hospitals	0 - 15	Not reported	Not reported	-	
	Fine et al. 1993(78)	4 hospitals	8.6 -16.4	0.32	13.0% (3.22)		
	Garau et al. 2008(86)	10 hospitals	1.1 – 19.7	< 0.001	8.73% (5.49)	-	
	Hedlund et al. 2002(88)	17 hospitals	0 - 6.6	Not reported	Not reported	-	No correlation between mean PSI and mean mortality rate (p=0.85)
	Iroezindu et al.(89)	4 hospitals	17.9 – 31.1	0.53	22.58% (6.06)	-	
	Klausen et al.(99)	22 hospitals	7 – 17	Identified 3 hospitals with higher IP mortality and one with lower (p <0.01)	11.59% (2.67)	Gender, age, ventilatory support, Chalson index score	>65 years only
	Laing et al. 2004(90)	2 hospitals	1.32 -2.35	0.8	Presented as range	-	
	Lave et al 1996(91)	8 regions	9.7 – 13.7	<0.1 for low and medium severity CAP	11.31% (1.29)	-	
	Remond et al. 2010(95)	2 geographic regions	0.6 - 1.6	>0.05	1.1%	-	
	Sow et al 1996(98)	2 hospitals	6 – 8	>0.5	7%	-	

Post discharge mortality	*Cabre et al. 2004(82)*	27 hospitals	0 – 13.0	<0.001	4.1%	-	14 days post discharge
	Capelasteg ui et al. 2005(83)	5 hospitals	8.1 – 11.1	0.93	9.74% (1.14)	-	30 days post admission
	Feagan et al. 2000(85)	20 hospitals	0 – 40.0	Not reported	14.76% (9.03	-	30 days post admission
	Fine et al. 1993(78)	4 hospitals	11.3-21.8	0.31	17.35 % (4.58)	PSI risk class, Age, NH resident, Race, Bacteraemia, Serum sodium <= 130 mmol/l, Hematocirt < 0.295, BUN >=10.7 mmol/l	6 weeks post discharge
	Gilbert et al. 1998(87)	4 hospitals	5.8 – 11.9	0.01	Not reported	Study site <u>not</u> statistically significant predictor of 30-day mortality in multivariate logistic regression controlling for patient demographics, severity at presentation and baseline site differences.	30 days post admission
	Klausen et al.(99)	22 hospitals	4 – 13	Two hospitals identified with higher mortality (p <0.01)	8.54% (2.24)	Gender, age, ventilatory support, Chalson index score	>65 years only. 30 days post discharge
	Laing et al. 2004 (90)	2 hospitals	1.97 – 2.35	0.5	Presented as range	-	30 days post admission
	Remond et al. 2010 (95)	2 geographic regions	0.7 – 0.9 (30 day post admission)	>0.05	Presented as range	-	30 days post admission

Re-admission following discharge	*Cabre et al. 2004 (82)*	27 hospitals	0 – 8.7	0.004	2.3%	-	Unspecified
	Gilbert et al. 1998 (87)/ McCormick et al. 1999 (93)	4 hospitals	7.4 – 14.1	0.08	Not reported	-	30 days post admission
			5 – 13	0.03	9% (3.65)	-	14 days post discharge
	Klausen et al. (99)	22 hospitals	7-17	Effect parameterization in Cox regression analysis identified 3 hospitals with higher readmission rate ($p < 0.01$)	11.82% (2.46)	Gender, age, ventilatory support, Chalson index score	30 days post discharge
	Laing et al. 2004 (90)	2 hospitals	3.62 – 4.12	0.5	Presented as range	-	30 day readmission
	Remond et al. 2010 (95)	2 geographic regions	6.7 – 13.8 (all cause)	<0.05	Presented as range	-	28 day readmission
			2.4 – 6.9 (respiratory)	>0.05	Not reported	-	
	Reyes Calzada et al. 2007 (96)	4 hospitals	4.6 – 10.3	0.6	7.68% (2.36)	-	30 days post discharge

Table 2.2 – Presented range of inter-hospital outcome measures across studies with p values and calculated mean and SD where possible. LOS- Length of Stay NA- not available

2.3.2.2 Mortality post discharge

Mortality following discharge was reported by fewer studies (n=8); one study reported mortality 14 days post discharge (82), six reported 30-day post-*admission* mortality (83, 85, 87, 90, 95, 99) and one reported six-week mortality only (78). Statistically significant differences were found in 3 of 7 studies that reported unadjusted p values (Figure 2.2, Table 2.2) (82, 87, 99). Three studies presented results adjusted for demographic and clinical variables (78, 87, 99); one study identified sites with statistically significant higher mortality (99).

2.3.2.3 Length of Stay

Fourteen studies reported on variation in LOS (78, 82-86, 88-91, 93, 95, 96, 99). The range in LOS variation (reported by 12 studies) was 0 to 14.7 days (mean 4.83 days, SD 3.89). Of nine studies reporting a range and p-value, all found statistically significant variation (Figure 2.3, Table 2.2) (78, 82, 83, 86, 90, 91, 93, 96, 99); six adjusted for confounders (78, 82, 83, 91, 93, 99). One additional study reported in text that following adjustment for confounders the risk of having a LOS greater than the mean for the study population was significantly increased for two hospital sites by 2-3 fold (89).

Figure 2.3 - Interhospital variation in length of stay

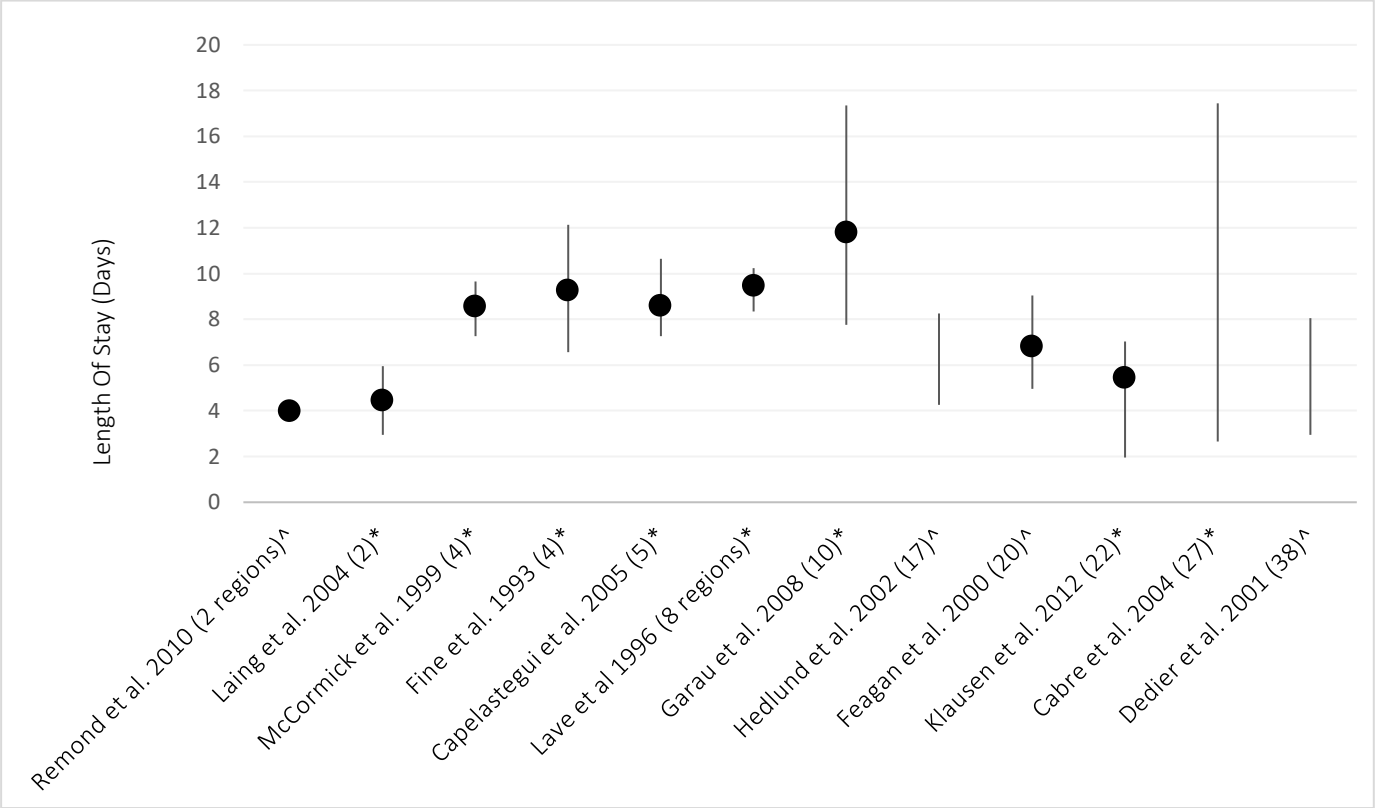


*Figure 2.3 - Inter-hospital variation in average LOS in days across studies where reported. Range represented as line, dot represents mean value where possible. * denotes a statistically significant result. ^ denotes no reported p value. The number in brackets represents the number of hospitals compared in the study, unless otherwise stated.*

The contribution of different factors towards variation in LOS was examined by 4 studies, each comparing inter-hospital variation (Table 2.3) (78, 82, 85, 90). These studies were able to account for 21%-61% of the total observed variation using statistical models adjusted for hospital site and different patient and disease characteristics. They found that the hospital of admission accounted for between 1 – 24% of the observed variation in LOS. The proportion of the total variation identified by each study due to hospital admission site (calculated as the variation accounted for by hospital site / the total variation accounted for by the model x 100) ranged between 1.6%-41.7%. No study adjusted the results for natural variation. Laing *et al*. attributed 26% of the observed variation in LOS to process of care measures. Duration of intravenous antibiotics and admission to ICU were also significantly associated with LOS in that study (90).

Table 2.3 - Contribution of hospital of admission to Variation in Length of Stay

Study	Number of hospitals	Adjusted for	**P value**	**Total Variation accounted for by the model (%)**	**Variation accounted for by hospital site (%)**	**Proportion of total variation accounted for by the model due to hospital site (%)**
Cabre et al. 2007 (82)	27	PSI risk class, Complications during hospitalisation, Admission to ICU, Oxygen therapy, Discharge to a NH	<0.001	28.99	12	41.5
Feagan et al. 2000 (85)	20	PSI, Smoking status, COPD or asthma, Bacterial pneumonia	Not reported	21	7	33.3
Fine et al. 1993 (78)	4	PSI risk class, Age, NH resident, Race, Bacteraemia, Serum sodium <= 130 mmol/l, Hematocirt < 0.295, BUN >=10.7 mmol/l	<0.0001	24	10	41.7
Laing et al. 2004 (90)	2	Patient factors: Age, Duration of fever, COPD, PSI, Cerebrovascular disease, Complications of pneumonia, Heart failure, Ethnicity, Bacteraemia, Diabetes Process of care measures:	<0.01	61 Of which: Patient factors – 34 POC measures – 26	1	1.6

		Duration of IV antibiotics, Admission to ICU, Antibiotic guideline adherence, Macrolide and beta-lactam				

Four studies examined whether variation in LOS was associated with variation in other clinical outcomes; none reported significant findings (78, 82, 83, 93). Specifically, a shorter LOS was not associated with increased mortality or readmission rates following multivariate analysis in two studies (82, 93). No study examined post-discharge patient-reported outcome measures (PROMs) in relation to LOS.

2.3.2.4 Readmission

Seven studies reported variation in the proportion of patients requiring re-admission for any reason (82, 87, 90, 93, 95, 96, 99); two from the same study population reporting readmission at differing follow up points (87, 93). Four found statistically significant differences (Figure 2.4) (82, 93, 95, 99). All results were unadjusted, except those from *Klausen et al*. who adjusted for gender, age, use of ventilatory support and Charlson index score, identifying three of 22 hospitals with increased re-admission rates (99).

Figure 2.4 - Variation in 30-day readmission rates

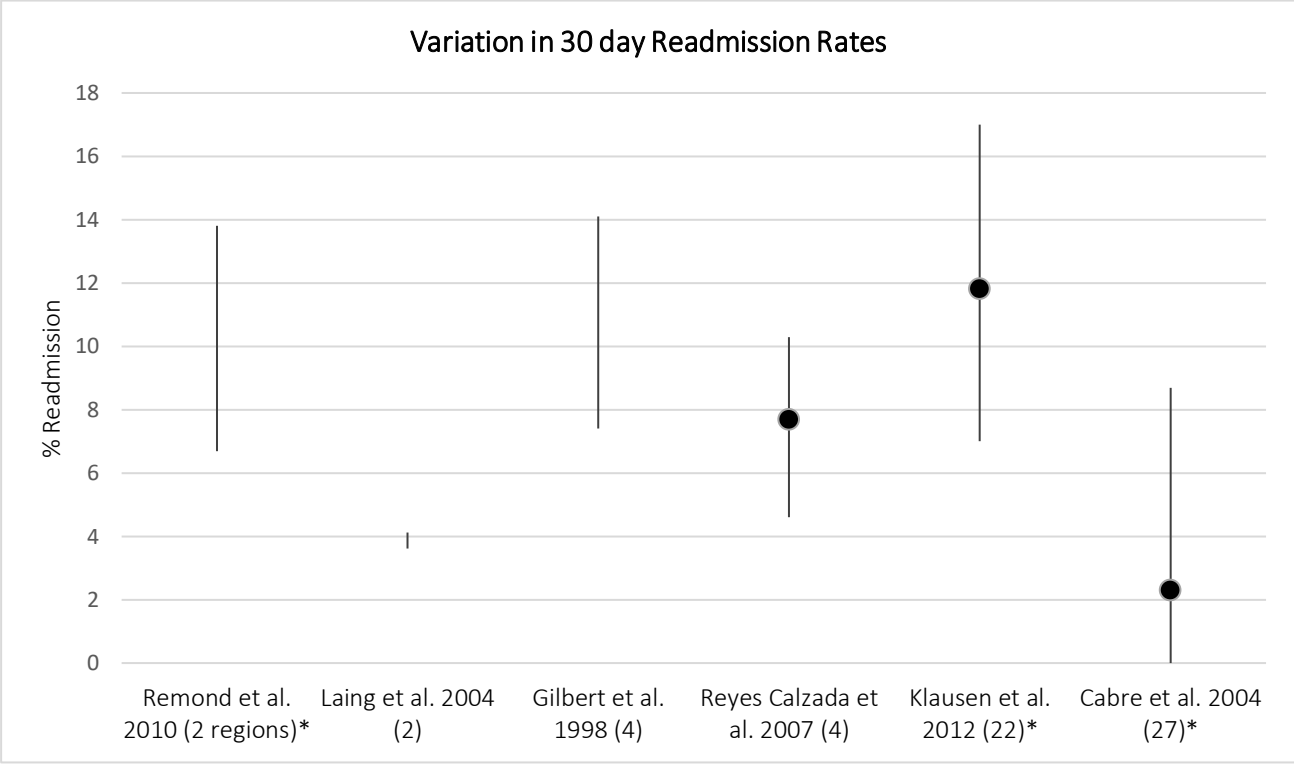


*Figure 2.4 - Inter-hospital variation in all cause readmission rates across studies. Range represented as line, dot represents mean value where possible. * denotes a statistically significant result. ^ denotes no reported p value. The number in brackets represents*

the number of hospitals compared in the study, unless otherwise stated. Data presented from McCormick et al. is 14-day post discharge readmission rates

2.3.3 Variation in Process of Care Measures

A wide range of process of care measures were reported across studies (Table 2.4). Variation in the proportion of patients admitted to ICU (n=7 studies) was found to be significantly different in the five studies that reported p-values for this outcome (78, 82, 83, 85, 91, 93, 95). Similarly, significant variation was observed in the proportions with blood cultures obtained on admission (2 of 4 studies reported p-values; both $p<0.05$) (80, 84, 95, 97); receiving antibiotics within 8 hours (2 of 4 studies reported p-values; both $p<0.05$) (80, 83, 84, 97) and duration of intravenous antibiotics (4 of 5 studies reported p values; all 4 $p<0.05$) (82, 83, 85, 87, 90). Seven studies examined variation in adherence to antimicrobial guidelines (4 of 7 studies reported p-values; 2 reported $p<0.05$) (83, 85, 90, 92, 95-97) while two studies examined variation in total antibiotic duration (83, 87); one found statistically significant variation (83). *Laing et al*. found significant variation in the duration of intravenous antibiotic therapy between two hospitals with no observed difference in mortality (90). Following variance analysis they accounted for 41% of the observed variation in IV antibiotic duration, attributing 24% to patient characteristics, 4% to other management variables and 13% to hospital of admission ($p<0.001$).

Table 2.4 - Variation in Process of Care Measures

Process of Care Measure	**Study**	**Number of units**	**Inter-hospital outcome range (%)**	**P value for difference between units**	**Mean (SD)**	**Comments**	**Statistically significant variation in Outcome Measures reported?**
Admission to ICU (%)	*Cabre et al. 2004 (82)*	27 hospitals	0 – 10.7	0.002	3.3		M, PDM, LOS, Readm
	Capelastegui et al. 2005 (83)	5 hospitals	0 – 7.3	0.03	3.36, (2.61)	-	LOS
	Feagan et al. 2000 (85)	20 hospitals	0.0 – 31.4	Not reported	13.33 (8.48)	-	
	Fine et al. 1993 (78)	4 hospitals	11.3 – 15.8	Not reported	NA	-	LOS
	Lave et al 1996 (91)	7 regions	14.4 – 18.1	<0.01	16.49 (1.24)	-	M, LOS

	McCormick et al. 1999 (93)	4 hospitals	6 – 25	<0.001	14.5 (8.10)	ITU admission within the first 24 hours	LOS
	Remond et al. 2010 (95)	2 geographic regions	1.8 – 23.8	<0.001	NA	-	Readm
Blood cultures obtained on admission (%)	*Arnold et al. 2013 (80)*	3 geographic regions	58 – 87	<0.001	69.3 (15.5)	-	M
	Dedier et al. 2001 (84)	38 hospitals	53.6 – 100	Not reported	NA	Obtained within 24 hours	
	Remond et al. 2010 (95)	2 geographic regions	56.7 - 93.0	<0.001	As presented by range	-	Readm
	Schouten et al. 2005 (97)	8 hospitals	48 -67	Not reported	57 (median)	2 sets of cultures	
Antibiotics within 8 hours of presentation (%)	*Arnold et al. 2013(80)*	3 geographic regions	71 - 86	<0.001	80 (7.9)	-	M
	Capelastegui et al. 2005 (83)	5 hospitals	59.6 - 84	<0.001	70.8 (10.8)	-	LOS

	Dedier et al. 2001 (84)	38 hospitals	53.8 – 100	Not reported	NA	-	
	Schouten et al. 2005 (97)	8 hospitals	36 – 87	Not reported	68 (median)	Within 4 hours of presentation	
Adherence to antimicrobial guidelines (%)	*Capelastegui et al. 2005 (83)*	5 hospitals	71.4 – 89.7	<0.001	83.4 (7.3)	-	LOS
	Feagan et al. 2000 (85)	20 hospitals (ATS guideline compliance)	47.9 - 100	Not reported	80.33 (14.0)	-	LOS
	Laing et al. 2004 (90)	2 hospitals	47 - 66	0.02	Presented as range	Severe cohort only	
	Malone et al. 2001 (92)	5 hospitals	16.7 -50	Not reported	30.7 (12.5)	Severe cohort only	
	Remond et al. 2010 (95)	2 geographic regions	16.3 – 28.7	<0.05	As presented by range	-	Readm
	Reyes Calzada et al. 2007 (96)	4 hospitals	53.4 – 84.6	0.0001	72.52 (15.1)	-	LOS
	Schouten et al. 2005 (97)	8 hospitals	5.0 - 59	Not reported	45 (median)	-	

Duration of IV therapy (days)	*Cabre et al. 2004 (82)*	27 hospitals	2.5 - 6.9 (mean)	0.001	4.6 (3.6)	-	M, PDM, LOS, Readm
	Capelastegui et al. 2005 (83)	5 hospitals	3 – 7.9 (mean)	<0.001	5.3 (1.9)	-	LOS
	Feagan et al. 2000(85)	20 hospitals	3.0 – 6.5 (median)	Not reported	5.2 (0.9)	-	
	Gilbert et al. 1998 (87)	4 hospitals	6.0 – 7.0 (median)	0.002	6.6 (0.58)	-	PDM
	Laing et al. 2004 (90)	2 hospitals	1.7 – 3.0 (mean)	0.001	Presented as range	-	LOS
Total antibiotic duration (days)	*Capelastegui et al. 2005 (83)*	5 hospitals	12.9 – 16.4 (mean)	<0.001	14.4 (1.3)	-	LOS
	Gilbert et al. 1998 (87)	4 hospitals	13.0 – 15.0 (median)	0.49	14 (0.8)	-	

Table 2.4 – Presented range of inter-hospital process of care measure achievement across studies with p values and calculated mean and SD where possible. LOS- Length of Stay NA- not available, M = Inpatient Mortality, PDM = post discharge mortality, Readm = Readmission

2.4 Discussion

Of the three primary outcome measures of interest, we found consistent evidence for significant variation in relation to LOS, but not mortality or hospital readmission rates. There was consistent evidence for inter-hospital variation in all process of care measures examined, however evidence linking variation in outcomes with variation in process of care measures was limited.

The evidence for variation in LOS was consistent across studies and maintained following case-mix adjustment for patient and disease factors. Despite this, reasons for variation were not identified. Only one study was able to account for over 30% of the total observed variation (90). Residual unaccounted variation may be attributed to i) unmeasured factors not included in the statistical models used or ii) natural variation due to chance. Multiple factors affect LOS, many of which were unmeasured within the studies (eg. physician behaviour, local healthcare system infrastructure) or competitively effect the direction of association (eg. better quality of care leading to survival of higher severity patients and ultimately a *longer* LOS). None of the studies used a statistical methodology to quantify or allow for natural variation in their analysis of LOS. Therefore, despite consistent evidence for variation, it is not possible to quantify what proportion is due to true differences between units rather than chance.

This review observed significant variation in in-patient mortality only in larger studies comparing five or more units. Where variation in mortality was observed, care in the interpretation of results is warranted as adequate adjustment for both case-mix and natural variation were limited. In addition, none of the studies in this review adjusted for social deprivation; a recognised major determinant of inequalities in health, including mortality. In a UK community study, 80% of the regional

variation in mortality from lower respiratory tract infections was accounted for by socio-demographic factors, as measured by the Index of Multiple Deprivation (100).

Only one study used a statistical method to control for the effect of natural variation when assessing variation in mortality; namely the Spiegaelhalter method used by *Aelvoet et al*. This method to identify outlying performing hospitals has been used elsewhere in national audit programmes to examine variation in healthcare (101). It is an alternative method to reliability adjustment in removing the 'chance' element from the analysis of variation. As a graphical method for assessing variation in outcomes it has advantages over institutional ranking as it plots where institutions lie within the 95% (2 standard deviation) and 99.8% (3 standard deviation) predication limits around the mean. It can identify institutions that consistently lie outside these limits for further investigation. It incorporates the institutional sample size into the funnel plots as a measure of reliability of each institutional prediction. *Aelvoet et al.* identified providers with consistently outlying results within their single country study suggesting true variation in mortality from CAP. Outside this study, it is difficult to quantify from available evidence the proportion of observed variation in mortality that is due to true differences between units.

Outcome measures are increasingly used to rank institutions inevitably giving the appearance of ranking quality of care (73). Rankability measures the proportion of the variation between providers with regards to an outcome that is due to true differences; it is considered high if above 70% (102). No study in this review directly assessed the rankability of LOS as an outcome measure in CAP. The proxy measure generated in this review suggests a low rankability of <50% across studies suggesting caution should be applied when making inferences about quality of care by ranking hospitals due to variation in LOS.

Although mortality is an important clinical outcome, it is a relatively infrequent outcome even in adults hospitalised with CAP; occurring in 10 – 15% of cases overall (16). Small sample size and low event rates limit the statistical power to compare between hospitals (103). Therefore, unless large sample sizes are obtained, mortality may be an insensitive marker to detect variation in care.

Many studies found CAP-related process of care measures to vary across hospitals. Evidence from observational studies suggests an association between selected clinical outcomes and certain process of care measures; a lower mortality has been associated with both earlier administration of antibiotics and obtaining blood cultures on admission while a decreased LOS has been associated with both antibiotic administration within four hours of admission and an appropriate switch from intravenous to oral antibiotics (104, 105). However, none of the studies in this review were able to fully examine the association between variation in process of care measures and variation in clinical outcomes.

2.4.1 Strengths and limitations

To overcome the lack of specific terminology identifying studies reporting on healthcare variation, we adopted a broad search criteria with additional hand searching of references to identify relevant studies. The quality of studies eligible for this review was moderate. However, due to inconsistencies in the statistical measures used across studies, meta-analysis was not possible and a structured synthesis was constructed. Reporting of the proportion of missing data and the subsequent handling of these data was absent in several studies, potentially reducing statistical power and introducing non-response bias to these studies.

Publication bias with studies observing minimal variation remaining unpublished is an important limitation. Such bias may account for the finding of variation in LOS in all relevant included studies. The majority of included studies were conducted in Europe or North America. Findings cannot be directly applied to health care systems in developing countries or other developed countries. Due to limited study numbers, results of studies reporting regional and inter-hospital differences were combined. Although limited to three studies, international differences in healthcare systems and populations served may bias results towards increasing observed variation.

2.5 Conclusions

In the management of adults hospitalised with CAP, there is consistent evidence of moderate quality for variation in LOS and process of care measures but not for in-patient mortality or hospital re-admission rates. Evidence linking variation in outcomes with variation in process of care measures was limited due to a lack of relevant studies. The proportion of observed variation due to chance is not quantified by existing evidence. This review highlights the importance of quantifying this in order to assess the validity of institutional (or regional) ranking by healthcare outcomes as a marker of quality of care in patients with CAP.

Chapter 3 - Outcomes following hospitalisation with community-acquired pneumonia - a descriptive analysis of British Thoracic Society national audit data 2018/19

3.1 Introduction

Since the introduction of BTS and NICE guidelines for management of adults with community-acquired pneumonia (CAP) in 2009 and 2014, six British Thoracic Society (BTS) national audits capturing data on adults hospitalised with CAP in the UK have taken place. The latest audit cycle took place in December 2018 – January 2019 (1, 34). Over this time-period, improvements in patient management and decreased inpatient mortality (from 20.2% to 10.4%) have been observed (16, 17). However, readmission amongst those that survive to discharge has increased from 10.5% to 14.3% (17). Both outcomes may be underestimated by audit data that is specific to the participating site and lacks integration with data from the community or other NHS Trusts. Readmissions occurring at Trusts other than the index admission Trust are not captured. In-patient 30-day mortality may not include deaths in the community; in the USA, nearly 50% of deaths within 30 days following admission with CAP occur after discharge (106). Although explored in other healthcare systems, limited UK data exist on causes for readmission or mortality following hospitalisation with CAP (23, 107). Understanding these may provide insights for potential quality improvement targets to further drive improvement in patient care in the UK.

Hospital Episode Statistics (HES) is a database managed by NHS digital that contains details of all hospital admissions to NHS hospitals in England. It is used primarily to ensure payment to hospitals for care delivered. It holds data on admitted patient care episodes, critical care episodes and through a link with the Office of National Statistics (ONS), mortality data. As part of the latest national BTS audit 2018/19, individual case data were linked with corresponding HES data creating an enriched dataset.

3.1.1 Aims

The primary objectives of this work were to:

1) Describe the linked BTS/HES audit cohort and compare basic demographics and outcomes with high-level non-audit HES data from patients with pneumonia during the same time-period.
2) Characterise the cohort readmitted within 30 days of discharge following their index admission with CAP and describe the reasons for readmission.
3) Describe the audit cohort using the enriched outcome data; specifically, ninety-day mortality and recorded cause of death.

3.2 Methods:

3.2.1 BTS CAP Audit Cohort

This is a retrospective analysis of data from the British Thoracic Society (BTS) national adult CAP audit collected between 1/12/18 - 31/1/19. Methodology and findings from the national audit have been reported previously (17). In brief, cases were identified by participating institutions via ICD10 codes mapping to a primary discharge diagnosis of pneumonia (J12.0-J18.0 inclusive) and selected for eligibility against inclusion criteria to confirm a clinical and radiographic diagnosis of CAP. The audit defines a case of CAP as an immunocompetent adult (≥16 years) hospitalised with symptoms of a lower respiratory tract infection, treated for CAP by the admitting clinicians with accompanying acute infiltrates consistent with pneumonia on admission chest radiograph (CXR). Cases are excluded by participating sites if they have been discharged from hospital in the ten days prior to their index admission, are transferred from another hospital provider or diagnosed as immunocompromised or with aspiration pneumonia.

3.2.2 Linked BTS Audit and HES Dataset

Requirement for patient consent to collect identifiable information was waived prior to data collection following successful section 251 application to the Confidential Advisory Group (reference number 18/CAG/0147). Cases were entered into the audit by participating institutions via the secure online BTS audit tool. Data fields collected included: patient identifiers (hospital number, date of birth), demographic information, details of pre-existing co-morbid disease, index disease severity, investigations performed, treatment given and patient outcomes. Through NHS digital, unique hospital identifiers were linked to individual case records in the HES admitted patient care (APC) and critical care (CC) datasets via the HESID.

The index CAP admission was matched with a HES admission spell by NHS Digital using the admission date provided in the audit dataset. Additional data fields obtained from HES included geographical details, index of multiple deprivation (IMD) score, ICD10 diagnoses and where applicable, critical care admission details. Linked mortality data from those who died were obtained through the HES linked Office of National Statistics (ONS) dataset via NHS digital. Mortality data obtained were: i) the main cause of death (ICD10 code), ii) all ICD10 diagnosis codes recorded as a cause of death, and iii) 30 and 90-day from index admission mortality indicators. The main cause of death is defined as the medical condition judged to be the underlying cause of death (108).

3.2.3 Definition of readmission and ICD10 outcome codes

A readmission was defined as an emergency admission to any hospital within 30-days of index discharge. Hospital spells starting <1 day following index discharge were not counted and elective readmission spells were excluded. Diagnosis on readmission and cause of death were assessed using ICD-10 version 2019 codes (109). These were divided into three categories: pneumonia, respiratory (non-pneumonia) and non-respiratory causes (Table 3.1). As per the BTS audit definition of CAP, ICD10 codes J12-J18 inclusive denoted pneumonia. The respiratory non-pneumonia category was defined using ICD10 codes for intrathoracic malignancy (C33-34, C38-39) and diseases of the respiratory system (J00-J99), excluding codes denoting disease of the upper respiratory tract (J30-J39) and the codes used to define pneumonia (J12-J18). All other ICD10 codes were included in the non-respiratory category and further sub-categorised by organ system involved (Table 1). ICD10 codes denoting the reason for readmission were identified from the primary diagnosis code on the final episode of the readmission spell.

Table 3.1 - ICD10 codes for non-respiratory diagnoses

Diagnosis Category	**ICD-10 version 2019 codes**	**ICD10 Diagnostic group**
Non-respiratory infections	A00-A99 B00-B99	Infectious and parasitic diseases
Malignancy (non-thoracic)	C00-C32, C37, C40-97	Malignant neoplasms
Haematological disorders	D50-89	Diseases of the blood and blood-forming organs
Endocrine disease	E00-E90	Endocrine, nutritional and metabolic disorders
Neurological disease	F00-F99 G00-G99	Mental and behavioural disorders Diseases of the nervous system
Cardiovascular disease	I00-I99	Diseases of the circulatory system
Gastrointestinal disorders	K00-K93	Disease of the digestive system
Renal disease	N00-N99	Diseases of the genitourinary system
Trauma & Orthopaedics	S00-S99	Injury due to external causes
Symptom Code	R0-94	Symptoms, signs and abnormal findings not elsewhere classified
Rheumatology or dermatological disease	L00-L99 M00-M99	Diseases of the skin and subcutaneous tissue Diseases of the musculoskeletal system and connective tissue

3.2.4 High-level HES data

In addition to the linked dataset, high-level demographic and outcome data of adults admitted during the audit timeframe with a primary diagnosis of pneumonia (ICD10 codes J12-J18) to each NHS provider in England were obtained from HES. These were available as appropriate summary statistics on a Trust level and also provided following exclusion of cases in the HES/BTS linked dataset. To avoid de-anonymization, data were not available from providers with less than 10 cases meeting the criteria. This high-level data represents a cohort of cases who, prior to case note review by a clinician at a participating site, meet the audit criteria based on ICD10 code and age alone. Previous work demonstrated that the proportion of these cases who would be eligible for inclusion in the audit is 54.1% (IQR

44.8-64%), varying by Trust (17). The most common reason for failing to meet inclusion criteria is the absence of infiltrates on CXR.

3.2.5 Statistical Analysis:

Firstly, a comparison of the high-level HES demographic and outcome data with BTS cohort data were performed and appropriate summary statistics across the Trusts calculated. Secondly, a descriptive analysis of the linked dataset was performed; appropriate summary statistics for normally and non-normally distributed data and the frequency of causes of death and readmission calculated. Characteristics of readmitted cases were compared to those not readmitted using appropriate summary statistics. All analyses were performed using STATA version 16.0.

3.3 Results

3.3.1 Comparison of high-level cohort data from the BTS and HES cohorts

From HES, high level demographic and outcome data on cases admitted during the audit period (1/12/18-31/1/19) with a primary diagnosis (ICD 10 code J12-J18) of pneumonia were available from 170 NHS providers. Providers with small case numbers (<10 cases) were suppressed and removed, leaving data from 152 providers for analysis.

The HES cohort was older (78 vs 75 years) with a higher proportion of men (56% vs 47.6% male) (Table 3.2). There was no difference in the Trust median length of stay or proportion admitted to intensive care between cohorts. Both inpatient 30-day mortality (13.0% vs 10.0%) and total 30-day mortality (17% vs 12.5%) are higher in the HES cohort than the BTS cohort. The highest mortality observed was in the HES excluding BTS cohort (18.0% 30-day mortality).

Table 3.2 - Comparison of demographics and outcomes between HES only cohort and BTS audit cohort

	BTS audit cohort		**HES cohort**	
	By cohort % (SD)	**By trust % (SD)**	**All J12-J18 admissions by Trust % (SD)**	**Excluding BTS audit cohort by Trust % (SD)**
Number of providers	121	121	152	152
Number of cases per Trust Median (IQR)	66 (52-110)	66 (52-110)	360 (255-495)	308 (213.7-436.2)
Age Median (IQR)	75 (61-85)	75 (72.5-78)	78 (76-79.1)	78 (77-80)
Gender (% male)	47.6	47.6 (7.01)	56 (5.8)	55 (5.7)
Length of stay in days Median (IQR)	5 (2-8)	5 (4-5)	5 (4-6)	5 (5-6)
Critical care admission	5.2	5.3 (4.0)	5 (7.6)	5 (7.3)
Total mortality at 30-days	13.6	12.5 (6.6)	17 (3.35)	18 (3.8)
Inpatient 30-day mortality	10.4	10.0 (6.1)	13 (2.8)	14 (3.2)

3.3.2 Description of BTS-HES linked cohort

Of 10,196 cases entered in the audit, linked HES data were available in 9,293 and ONS mortality data were available in 2,790 of these cases. Accuracy of matching the HES and BTS data were good; 8,552 (92%) of index admission episodes were matched at rank 1 (n = 9,048, 97.4% at rank 1-3). Of those matched, HES data were missing in 46 cases (<0.5%). The median number of episodes per spell for index admissions was two (IQR 1-3, range 1-13). The ICD10 code on discharge included a J12-J18 code in 8,939 (96.7%) of index admissions.

The lower super output area of residence was available in 9,217 (99.2%) of cases. Of these, 7,498 cases (81.4%) resided in urban areas defined as

having a population of 10,000 or more with a less sparsely populated wider surrounding area. The mode of admission in 8,326 (89.6%) of cases was via the Emergency Department (ED) whilst 661 (7.1%) were admitted via the GP. The most common treating specialty of the consultant of the admission episode was general medicine (n = 7537, 81.1%) followed by respiratory (n = 1147, 12.3%). Of those hospitalised, 7,671 (92.3%) were discharged to their usual residence.

Procedures performed during admission were available from HES and coded using Classification of Surgical Operations and Procedures (OPCS4) codes. Of 9,247 cases with available data, 933 (10.1%) had a CT chest or CT Pulmonary angiogram, 160 (1.72%) had a pleural procedure and 51 (0.55%) had a bronchoscopy during their index admission.

3.3.3 Readmission

3.3.3.1 Characteristics of the readmitted cohort

From the HES data obtained on the 8,316 cases that survived to discharge, 1,304 (15.7%) had emergency readmissions within thirty-days of discharge. This is higher than the rate recorded in the BTS audit (14.0%). Two hundred and thirty-eight (2.9%) patients were readmitted multiple times within 30-days. The median number of days between index discharge and first readmission was nine days (IQR 4-17.5). The majority of readmissions were through ED (n = 1089, 83.5%).

Those readmitted were older (78 vs 73 years) with more co-morbid disease and more likely to have had severe disease during their index admission (28.1 vs 20.2%) (Table 3.3). The proportion of patients with observations within 24 hours prior to discharge suggesting clinical instability was similar in those readmitted and not (13.9% vs 12.3%, p=0.14). The median LOS for the index admission was longer in those readmitted than not (5 vs 4 days). The median readmission LOS was 4 days (IQR 1-10) and inpatient mortality was 10.2% (n=133).

Table 3.3 - Characteristics of readmitted and not readmitted cases

	Readmitted N (%)	**Not readmitted N (%)**	**P value**
Demographics	1304 (15.7)	7012 (84.3)	
Median age (IQR)	78 (66-86)	73 (58-83)	**<0.001**
Gender (male)	642 (49.2)	3331 (47.5)	0.24
IMD quintile – data available:	1294 (99.2)	6918 (98.7)	
1 (least deprived)	173 (13.4)	1056 (15.3)	
2	243 (18.8)	1243 (18.0)	
3	261 (20.2)	1423 (20.6)	
4	270 (20.9)	1511 (21.8)	
5 (most deprived)	347 (26.8)	1685 (24.4)	0.18
Co-morbid disease:			
Cardiac failure	189 (14.5)	573 (8.2)	**<0.001**
Other chronic cardiac disease	408 (31.3)	1697 (24.2)	**<0.001**
Cerebrovascular disease	143 (11.0)	609 (8.7)	**0.01**
Liver disease	31 (2.4)	88 (1.3)	**0.002**
Chronic kidney disease	146 (11.2)	603 (8.6)	**0.003**
Malignancy	123 (9.4)	449 (6.4)	**<0.001**
COPD	417 (32.0)	1679 (23.9)	**<0.001**
Other chronic lung disease	238 (18.3)	1124 (16.0)	**0.05**
Diabetes	255 (19.6)	1199 (17.1)	**0.03**
Dementia	163 (12.5)	674 (9.6)	**0.001**
BMI over 40	18 (1.4)	70 (1.0)	0.22
Severity:			
Mild	451 (38.5)	3247 (50.3)	
Moderate	391 (33.4)	1901 (29.5)	
Severe	329 (28.1)	1303 (20.2)	**<0.001**
Missing data	133	561	
Index admission:			
Length of Stay	5 (3-9)	4 (2-8)	**<0.001**
Critical care admission	49 (3.8)	283 (4.0)	0.68
Clinical Instability on discharge observations*	162 (13.9)	801 (12.3)	0.14
Length of IV antibiotic course – data available	1095 (84.0)	5975 (85.2)	
<24 hours IV antibiotics	235 (21.5)	1447 (24.2)	
24-72 hours antibiotics	408 (37.3)	2207 (36.9)	

>72 hours antibiotics	452 (41.3)	2321 (38.8)	0.11

*IV = intravenous *Clinical instability defined at ≥1 of: HR≥100, RR≥24, T≥37.8, SBP<90 or SpO2<90 or <86 in those with and without COPD respectively in the final observations prior to discharge. Data were available in 1168 and 6509 of those readmitted and not readmitted.*

3.3.3.2 Respiratory causes of readmission

The primary readmission diagnosis was respiratory disease in 769 (59.0%) cases (Table 3.4); 497 (38.1%) were due to pneumonia (ICD10 codes J12-18). COPD was the second most common respiratory cause (n=87, 11.3% of respiratory readmissions) (Table 3.5). In those with pneumonia on readmission, the median number of days between index discharge and readmission was shorter than readmissions for other causes (7 vs. 11 days). An ICD10 code denoting hospital-acquired infection (Y95) was associated with a higher proportion of readmissions with pneumonia than other diagnoses (22.1% vs 4.3%). ICD10 codes indicating complications of pneumonia (pleural effusion, empyema and pulmonary abscess) were the primary diagnosis in 36 cases (4.3% of respiratory readmissions). Readmissions with pneumonia were more likely to die during their readmission spell than readmissions due to other causes (15.1% vs 7.2%; OR 2.30 95% CI 1.39-3.31).

Table 3.4 - Reasons for readmission within 30-days of discharge and outcomes by category

Reason for readmission	**N (%)**	**Days between index discharge and readmission**	**Readmission outcomes**	
			Length of stay	**Inpatient death**
All readmissions	**1304**	**9 (4-17.5)**	**4 (1-10)**	**133 (10.2)**
Pneumonia (J12-18)*	497 (38.1)	7 (3-15)	5 (2-11)	75 (15.1)
Respiratory causes^ (excluding J12-18)	272 (20.9)	11 (5-19)	4 (2-9)	16 (5.9)
Non-respiratory causes	535 (40.0)	11 (5-19)	4 (1-10)	42 (7.8)
Of which:				
Cardiovascular disease	99 (18.5)			
Symptom code	97 (18.1)			
Infection (non-respiratory)	53 (9.9)			
Renal disease	52 (9.7)			
Gastrointestinal disease	49 (9.2)			
Trauma & Orthopaedic	39 (7.3)			
Rheumatology or dermatological disease	39 (7.3)			
Other	28 (5.2)			
Neurological disease	28 (5.2)			
Malignancy (excluding thoracic)	20 (3.7)			
Endocrine disease	20 (3.7)			
Haematological disorder	11 (2.1)			

Non-respiratory causes categorised according to ICD-10 version 2019 code (Table 3.1)

Table 3.5 - Respiratory reasons for readmission

Table 5: Respiratory reasons for readmission		
ICD10 code*	**ICD 10 diagnosis**	**N (%)**
J12-18	Pneumonia	497 (64.6)
J44	COPD	87 (11.3)
J20-22	Other lower respiratory tract infection	43 (5.6)
J10-11	Influenza	32 (4.2)
J69	Aspiration pneumonitis	30 (3.9)
J90	Pleural effusion	15 (2.0)
C34	Lung cancer	12 (1.6)
J85-86	Abscess or empyema	12 (1.6)
J84	Interstitial pulmonary fibrosis	10 (1.3)
J96	Respiratory failure	8 (1.0)
J45-46	Asthma	6 (0.8)
J47	Bronchiectasis	5 (0.7)
J43	Emphysema	4 (0.5)
	Other respiratory	3 (0.4)
J92-94	Pleural disease	2 (0.3)
J06	Upper respiratory tract infection	2 (0.3)
J67	Hypersensitivity pneumonitis	1 (0.1)
Total		**769**

**ICD-10 version 2019 codes (109)*

3.3.3.3 Non-respiratory causes of readmission

Non-respiratory causes accounted for 535 (40.0%) of readmissions; diagnoses were varied with 238 ICD10 codes listed as the primary diagnosis code on the discharge episode of the admission spell. ICD10 codes denoting cardiac disease (n=99, 18.5%), symptom codes (n=97, 18.1%) and non-respiratory infection (n=53, 9.9%) were the most common non-respiratory codes (Table 3.6). The most common single codes denoted sepsis (A40-41), cardiac failure (I50-51) and urinary tract infection (N39).

The second diagnoses codes were examined in those with a primary sepsis code (A40-41); 17 (42.5%) had an ICD10 code indicating pneumonia (J12-18). When included as pneumonia readmissions, the rate of readmissions due to pneumonia increases to 39.6% (n = 517) with no significant change to other outcomes.

Table 3.6 - Fifteen commonest non-respiratory ICD10 codes associated with readmission

	ICD 10 codes*	**Diagnosis**	**Frequency (% of non-respiratory readmissions)**
1	A40-41	Sepsis	40 (7.48)
2	I50-51	Cardiac failure	37 (6.92)
3	N39	Urinary tract infection, site not specified	23 (4.30)
4	N17	Acute renal failure	21 (3.93)
5	R07	Chest pain	17 (3.18)
6	I44-49	Arrhythmia	16 (2.99)
7	R29	Tendency to fall, not elsewhere classified	16 (2.99)
8	L03	Cellulitis	12 (2.24)
9	I26	Pulmonary embolus	11 (2.06)
10	I20-25	IHD	10 (1.87)
11	K92	Gastrointestinal haemorrhage	10 (1.87)
12	F00-05	Dementia or delirium	10 (1.87)
13	R05-06	Cough, dyspnoea or wheeze	9 (1.68)
14	A04-09	Gastroenteritis and colitis of unspecified origin	9 (1.68)
15	I95	Hypotension	8 (1.50)

**ICD-10 version 2019 codes (109)*

3.3.4 Mortality

At the point of data extraction in May 2020, 2,790 of the 9,293 cases with HES linked data had died and ONS data on cause of death were available. Of these, 1207 (13.0%) and 1661 (17.9%) died within 30 and 90-days of their index admission date. This is higher than the BTS audit collected measure of inpatient mortality within 30-days of index admission (n= 977, 10.5%) reflecting the inclusion of both inpatient and community deaths.

3.3.4.1 Mortality within 90-days

An ICD 10 code denoting a diagnosis of pneumonia (J12 to J18 inclusive) was the main cause of death in 337 (20.2%) of those who died within 90-days (Table 3.7) and listed as contributing to the death in 1,079 (65.0%). The most frequent ICD10 pneumonia code listed as a main cause of death was *Pneumonia, unspecified* (J18.9; n=272, 80.7%; Table 3.8). Other respiratory causes made up 31.8% (n=528) of the deaths within 90-days; chronic obstructive pulmonary disease, lung cancer and interstitial pulmonary disease were the most common after pneumonia (Table 3.9). The most common non-respiratory causes were cardiac in all age groups, neurological in cases ≥ 75 years and extra-thoracic malignancy in those < 75 years (Table 3.10).

Table 3.7 - Cause of death by time period following index admission with CAP

Main cause of death	**Within 30 days N (%)**	**Within 90 days N (%)**
Total deaths	**1207**	**1661**
Pneumonia (J12-18)*	290 (24.0)	337 (20.2)
Respiratory causes^ (excluding J12-18)	395 (32.7)	528 (31.8)
Non-respiratory causes	522 (43.2)	796 (47.9)
Of which:		
Neurological or Psychiatric disorder	165 (13.7)	241 (14.5)
Cancer (excluding lung)	135 (11.2)	201 (12.1)
Cardiac disease	117 (9.7)	186 (11.2)
Other	44 (3.7)	76 (4.6)
Gastrointestinal disorder	23 (1.9)	32 (1.9)
Renal disease	14 (1.2)	25 (1.5)
Diabetes & Endocrine diseases	13 (1.1)	19 (1.1)
Infectious Diseases	6 (0.5)	7 (0.4)
Haematological disease	5 (0.4)	9 (0.5)

**ICD 10 codes J12-18 inclusive, as used in the BTS audit ^As defined by ICD 10 codes denoting thoracic malignancy (C34, C38 & C39) or disease of the respiratory system (J00-J06, J09-J11, J20-22, J40-47, J60-J99) other than the pneumonia (J12-J18). Non-respiratory causes categorised according to ICD-10 version 2019 code (Table 1)*

Table 3.8 - J12 – J18 Cause of Death within 30 and 90 days

ICD10 code	**ICD 10 diagnosis**	**30-day**	**90-day**
J18.9	Pneumonia, unspecified	238 (82.1)	272 (80.7)
J18.0	Bronchopneumonia, unspecified	40 (13.8)	51 (15.1)
J18.1	Lobar pneumonia, unspecified	5 (1.7)	7 (2.1)
J15.4	Pneumonia due to other streptococci	3 (1.0)	3 (0.9)
J13	Pneumonia due to Streptococcus pneumoniae	2 (0.7)	2 (0.6)
J12.1	Respiratory syncytial virus pneumonia	1 (0.3)	1 (0.3)
J15.9	Bacterial pneumonia, unspecified	1 (0.3)	1 (0.3)
Total		**290**	**337**

Table 3.9 - Frequency of respiratory disorders as main cause of death within 30 and 90-days

Main cause of death (ICD 10 codes)*	**Within 30 days N (%)**	**Within 90 days N (%)**
Pneumonia (J12-J18)	290 (42.3)	337 (39.0)
Chronic obstructive pulmonary disease (J44.0, J44.1, J44.9)	189 (27.6)	253 (29.2)
Lung cancer (C34.3, C34.9)	75 (10.9)	119 (13.8)
Interstitial pulmonary disease (J84.1, J84.9)	44 (6.4)	52 (6.0)
Asthma (J45.9)	23 (3.4)	26 (3.0)
Bronchiectasis (J47)	21 (3.1)	25 (2.9)
Influenza (J10.0, J10.1, J11.0)	14 (2.0)	14 (1.6)
Unspecified acute lower respiratory infection (J22)	11 (1.6)	15 (1.7)
Pneumonitis due to food and vomit (J69.0)	4 (0.6)	6 (0.7)
Emphysema, unspecified (J43.9)	3 (0.4)	5 (0.6)
Hypersensitivity pneumonitis due to unspecified organic dust (J67.9)	3 (0.4)	3 (0.3)
Unspecified chronic bronchitis (J42)	2 (0.3)	2 (0.2)
Coalworker pneumoconiosis (J60)	2 (0.3)	2 (0.2)
Pneumoconiosis due to asbestos and other mineral fibres (J61)	2 (0.3)	2 (0.2)
Pyothorax without fistula (J86.9)	1 (0.1)	1 (0.1)
Respiratory failure, unspecified (J96.9)	1 (0.1)	1 (0.1)
Abscess of lung with pneumonia (J85.1)	0	1 (0.1)
Other specified respiratory disorders (J98.8)	0	1 (0.1)
Total	**685**	**865**

**ICD-10 version 2019 codes (109)*

Table 3.10 - Ten most common non-respiratory causes of death within 90 days subdivided by age

Number	Cases <75 years		Cases ≥75 years	
	Cause of death (ICD10)*	**N (%)**	**Cause of death (ICD10)***	**N (%)**
1	Malignant neoplasm: Breast, unspecified (C50.9)	14 (7.9)	Unspecified dementia (F03)	113 (18.3)
2	Atherosclerotic heart disease (I25.1)	8 (4.5)	Chronic ischaemic heart disease, unspecified (I25.9)	42 (6.8)
3	Malignant neoplasm of prostate (C61)	7 (3.9)	Alzheimer disease, unspecified (G30.9)	39 (6.3)
4	Malignant neoplasm of kidney, except renal pelvis (C64)	6 (3.4)	Vascular dementia, unspecified (F01.9)	36 (5.8)
5	Acute myocardial infarction, unspecified (I21.9)	6 (3.4)	Stroke, not specified as haemorrhage or infarction (I64)	28 (4.5)
6	Alcoholic liver disease, unspecified (K70.9)	6 (3.4)	Malignant neoplasm of prostate (C61)	25 (4.1)
7	Malignant neoplasm: Pancreas, unspecified (C25.9)	5 (2.8)	Acute myocardial infarction, unspecified (I21.9)	14 (2.3)
8	Unspecified dementia (F03)	5 (2.8)	Parkinson disease (G20)	13 (2.1)
9	Motor neuron disease (G12.2)	5 (2.8)	Malignant neoplasm: Breast, unspecified (C50.9)	12 (1.9)
10	Multiple myeloma (C90.0)	4 (2.2)	Urinary tract infection (N39.0)	12 (1.9)

**ICD-10 version 2019 codes (109)*

3.3.4.2 Mortality within 30-days

An ICD 10 code mapping to a diagnosis of pneumonia was listed as a cause of death in more deaths within 30 than 90-days (main cause 24.0% vs 20.2%; any cause 75.5% vs 65.0%) (Table 3.7). The most frequent cause of death at 30-days otherwise reflected findings at 90-days. The most frequent ICD10 pneumonia code listed as the main cause of death was *Pneumonia, unspecified* (J18.9; n=238, 82.1%; Table 3.8). Other respiratory diseases made up 32.7% (n=395) of the deaths within 30-days; chronic obstructive pulmonary disease, lung cancer and interstitial pulmonary disease were the most common respiratory causes after pneumonia (Table 3.9).

3.4 Discussion

3.4.1 Key Findings

The most common reasons for readmission identified were pneumonia (38.1%), COPD (6.7%) and cardiovascular disease (7.6%), particularly cardiac failure. Inpatient mortality in those readmitted due to pneumonia was high; they were over twice as likely to die during readmission than those readmitted for other reasons (15.1% vs 7.2%; OR 2.30). Causes of death at 90-days were similar to reasons for readmission; 20.3% (n=337) pneumonia, 15.2% (n=253) COPD and 11.2% were due to cardiovascular disease. Neurological and malignant diseases were the most common non-respiratory cause of death in patients ≥75 years and <75 years respectively.

3.4.2 Comparison with published literature: Readmission

Published readmission rates within 30-days of discharge range from 7.3-20.1%, vary with healthcare system and are higher in older populations (107). At 15.7%, our observed readmission rate is at the higher end of this range, perhaps reflecting the older age of our cohort (median age 75 years). Over ten years of the national BTS CAP audit, readmission rates have increased by 3.8% (17). Emergency admissions across the NHS increased by 42% between 2006/07 and 2015/16, particularly in those ≥85 years of age or with multiple health conditions (110). Despite this, a retrospective analysis of readmission rates between 2006-16 across 150 hospital NHS Trusts reported no change in all-cause readmission rates (22). However, when subdivided by index admission category, the readmission rate following pneumonia increased by 2.72% (13.7% to 15.8%), similar to that observed in the national audit (22). Together, these findings suggest increasing readmission rates following pneumonia are disease specific and not simply reflective of a national trend.

Readmission is associated with significant mortality. In a study of UK emergency readmissions following an unscheduled index admission of any cause, *Shiue et al.* reported a 30-day mortality of 12.5% in those readmitted compared to 6.9% following the index admission (111). After adjustment for patient factors, the risk of death remained higher during readmission than index admission (aOR 12.36 vs 6.93). Studies in comparable healthcare systems consistently report pneumonia as the most common reason for readmission following hospital admission with CAP, responsible for 7.3% - 39.1% of all-cause 30-day readmissions (23, 24, 26, 107). Our observed rate (38.1%) is at the top end of this estimate; coding inaccuracies in the readmission diagnosis may falsely increase our rate (71). Consistent with previous studies, the other most common reasons for readmission observed were COPD, cardiovascular disease and infections (23-26, 107). In themselves, these are common reasons for emergency admission (112). Readmission with pneumonia, but not other causes, appears associated with significant inpatient mortality in our analysis (15.1% vs 7.2%; OR 2.30). Consistent with established risk factors, our readmitted cohort are older with more co-morbid disease (23, 25). Higher mortality might therefore be expected in this group, but not confined to those readmitted with pneumonia. Given the short period of time between index discharge and readmission in our cohort (7 days), the majority of readmission episodes with pneumonia likely reflect partial treatment or hospital-acquired infection rather than a recurrent CAP episode. Further work to clarify the cohort of patients readmitted with pneumonia and to develop strategies to prevent readmission are warranted.

3.4.3 Comparison with published literature: Mortality

Causes of death in our cohort mirror those observed in a study of adults with pneumonia in the USA (113). Mortensen et al. reported that 53% of deaths within 90-days were related to pneumonia, of which 76% occurred within 30-days (113). Neurological conditions, malignancy and cardiac conditions were responsible for 29%, 24% and 14% of deaths. Hospitalisation with CAP is associated with an increased risk of cardiovascular events (CVE). A systematic review in 2011 estimated CVE to occur in 17.7% (95% CI 13.9% - 22.2%) of inpatients with CAP (114). More recently, *Violi et al.* reported 32.2% of patients in their prospective cohort study experienced in-hospital cardiac events and found CVEs were associated with an increased risk of death (HR 5.49, $p<0.001$) (115). In a UK study examining deaths within 28 days of admission due to acute myocardial infarction (AMI), 12% were admitted primarily with a respiratory diagnoses (mostly pneumonia and COPD) (116). Most events occur within 30-days of admission with the risk maximal in the days following admission (117). Indeed, 62.9% (117/186) of deaths due to cardiovascular disease in our study at 90-days were within 30-days. Risk factors for CVE during admission with CAP include increasing age, hyperlipidaemia and severe CAP (117-119). The biological mechanism for increased cardiovascular risk is unclear; proposed mechanisms include host responses (including systemic inflammation and platelet activation) and *S. pneumoniae* invasion of the myocardium and subsequent cardiac scarring (120, 121). Taken together, cardiovascular disease is an important cause of both adverse outcomes and clinician awareness is advised.

3.4.4 Strengths and Limitations

The main strength of this work is the linkage of two comprehensive datasets (HES and BTS) including cases with a defined population of CAP. There is no single ICD10 category for CAP. Previous work has

demonstrated that the accuracy of a coded diagnosis of CAP is 63.3%, with over half of ineligible cases not meeting radiological inclusion criteria (17). The BTS audit cohort provides comprehensive clinical data on patients hospitalised with a clinical and radiological diagnosis of pneumonia; the effect of miscoding during the index CAP admission is, therefore, minimised (71). Linkage to HES/ONS data allows robust assessment of outcomes, capturing those occurring after index discharge.

Limitations of HES data include: coding variation, sensitivity to admission thresholds and quality of internal linkage (122). Despite centrally issued coding rules and financial incentives for accurate reimbursement driving improved accuracy, coding practices vary between hospitals, particularly secondary diagnosis and co-morbidity data (71, 123, 124). The overall accuracy of primary diagnosis codes used in our analysis of readmission, is fair (80.3%) (125). Data on ED attendances not resulting in admission (re-consultation) are not recorded in HES APC data; our results therefore underestimate the burden healthcare re-consultation in the secondary care setting and may be sensitive to variation in readmission thresholds. Individual case data are linked within HES using a HESID linkage algorithm that relies on accurate recording of the NHS number to avoid missed matches. Testing of this algorithm has demonstrated a low rate of false matches but estimated a missed-match rate of 4.1% (126). In our cohort, missed matches could lead to an underestimation of the true readmission rate. Reasons for readmission in missed matches are not expected to differ from the observed data.

The main limitation of the BTS audit dataset is missing clinical data occurring due to reliance on clinical teams for data collection. Differences between those with and without missing data in clinical or disease

characteristics that are derived solely from the BTS dataset cannot be completely excluded. The effect of missing outcome data is minimised by linkage with HES data. The proportion of missing data in HES is generally low (<1%) however varies by data field. For example, the proportion of patients with a known ethnicity in HES is low (<80%), limiting the utility of these fields (127).

The findings from analysis of the combined dataset may not be applicable to devolved nations or other healthcare systems; HES data for linkage was only available with audit data collected from England. Outcome data regarding healthcare utilisation in the community is not captured but presents a significant burden; the estimated re-consultation rate following discharge in patients with pneumonia is high (65.7%) with the majority of episodes occurring through the GP (90.1%) (128). Of note in our cohort, the admission route for the majority of observed readmissions was through ED (83.5%) rather than via the GP. The combined dataset lacks detailed data on prescribed antibiotic treatment courses and robust aetiological data, including antimicrobial resistance.

Chapter 4 Variation in healthcare outcomes of adults hospitalised with community acquired pneumonia: BTS National Community Acquired Pneumonia (CAP) Audit analysis

4.1 Introduction

Geographical variation in clinical care is considered ubiquitous across all aspects of healthcare (53). A proportion of this observed variation in healthcare measures is warranted, reflecting true differences in individual healthcare preferences and the demographics of the local population served. Conversely, persistent unwarranted variation in clinical care directly impacts on equity of services, population outcomes and use of resources (53). Outcome measures are increasingly used to rank healthcare between regions and hospital providers however there is concern that such ranking does not account for natural variation between units (72, 73).

The age-standardised mortality rate for pneumonia varies internationally with estimates suggesting the UK has the third highest mortality rate in Europe (10). The NHS Right Care Atlases of Variation in Healthcare for people with respiratory disease have highlighted persistent geographical variation in healthcare outcomes for pneumonia across the UK (49, 56). In 2019, the reported mortality rate differed by 2.8 fold (difference between 29.5-83.2 per 100 000 population) between areas whilst a 3.5-fold difference in median LOS (2-7 days) and proportion of 0-1 day admissions (11.1-38.5%) were also observed (56). Little is known about the causes of this apparent variation, to what extent it is unwarranted and whether ranking by outcome measures reflects true differences in care.

4.1.1 Objectives:

The primary objective is to describe variation between NHS Trusts in healthcare outcomes of adults hospitalised with community-acquired pneumonia (CAP) across England after adjustment for case-mix and accounting for natural variation.

The secondary objectives were: i) to describe variation of key process of care (POC) measures derived from CAP treatment guidelines, ii) where possible, to examine any association between variation in outcomes and variation in process of care measures, and iii) to assess the extent to which observed variation of outcome measures is due to chance.

4.2 Methods

4.2.1 Details of the study cohort

This is a retrospective analysis of aggregate data from six British Thoracic Society (BTS) national adult CAP audits (December and January 2009/10, 2010/11, 2011/12, 2012/13, 2014/15 and 2018/19). In each audit cycle, cases were identified by participating Trusts via ICD10 codes mapping to a primary discharge diagnosis of pneumonia (J12.0-J18.0 inclusive) and selected for eligibility against inclusion criteria to confirm a clinical and radiographic diagnosis of CAP. The audit defines a case of CAP as an immunocompetent adult (≥16 years) hospitalised with symptoms of a lower respiratory tract infection, treated for CAP by the admitting clinicians with accompanying acute infiltrates consistent with pneumonia on admission chest radiograph (CXR). Cases are excluded if they have been discharged from hospital in the ten days prior to their index admission, are transferred from another hospital provider, immunocompromised or diagnosed as aspiration pneumonia. The dataset holds data regarding patient demographics, pre-existing co-morbidities, disease severity, diagnosis, treatment and outcomes. The audit cohorts have been described in full previously (17, 129).

4.2.2 Unit of Variation

A unit of variation was defined as a single NHS acute hospital Trust. A Trust was chosen rather than hospital to minimise potential bias from split site Trusts with multiple participating hospitals providing differing or specialist services. A case is attributed to the NHS Trust of admission during the patient's hospitalisation with pneumonia. Where Trusts have merged over the audit timeframe, cases are included within the NHS Trust as per the time of the most recent audit (winter 2018/19). For the primary analysis, Trusts were excluded if they had not participated in the most

recent audit cycle (winter 18/19) or if they had entered <50 cases over all audit cycles.

4.2.3 Outcomes and Process of Care Measures examined

For the primary analysis, the healthcare outcomes assessed were: i) thirty-day inpatient mortality, ii) critical care admission, iii) readmission within 30 days of hospital discharge, iv) median length of stay (LOS), v) LOS ≤1 day, and vi) LOS>10 days (surviving cohort only included for readmission and LOS outcomes).

Key process of care measures were derived from established guidelines on the management of CAP and national audit quality improvement objectives (1, 17, 34). These were: i) time to first CXR, ii) time to first antibiotic, iii) guideline concordant antibiotic use, and iv) CAP bundle concordant care. Bundle concordant care in an individual was achieved if all of the following POC measures were achieved: i) CXR within 4 hours on admission, ii) antibiotics within 4 hours of admission, and iii) the use of guideline concordant antibiotics (77).

4.2.4 Sub-analysis on HES linked dataset

A sub-analysis using HES-ONS linked data from the most recent BTS audit cycle (winter 2018/19) was performed. Data from HES are available for England only; Trusts from devolved nations were excluded and those with less than 20 cases in the most recent audit were excluded. Thirty and ninety-day mortality from linked Hospital Episode Statistics (HES) and Office for National Statistics (ONS) mortality data capturing both hospital and community deaths were used as mortality outcomes. Other measures examined were informed by the results of the primary analysis.

4.2.5 Statistical Methods

The choice of statistical methods used in this work were informed by the findings of the Systematic Review presented in Chapter 2. This found no consistent methods for assessing variation in outcomes and that very few

studies adopted methodology accounting for natural variation. However, the best method used was the Spiegelhalter method as demonstrated by *Aelvoet et al.* to investigate interhospital differences in outcomes following admission with CAP in a single national health care system and clearly identified institutions with outlying results (79). We therefore replicated similar methodology in this work.

Crude proportions per trust of each healthcare outcome and the proportion adjusted for individual case mix were calculated. Appropriate summary statistics for normally and non-normally distributed data and minimum and maximum values are presented. Adjustment variables for each outcome examined were chosen following review of the literature and using Directed Acyclic Graph (http://dagitty.net/) (Figures 1-3) (130). Population characteristics adjusted for at an individual level were age, gender, presence or absence of a co-morbidity, disease severity (component parts of the CURB 65 score, except age) and audit year. For the winter 2018/19 sub-analysis outcomes 30 and 90-day mortality, deprivation as measured by the Index of Multiple Deprivation (IMD) from HES linked data was included as an adjustment variable.

Figure 4.1 - DAG for admitting trust and mortality

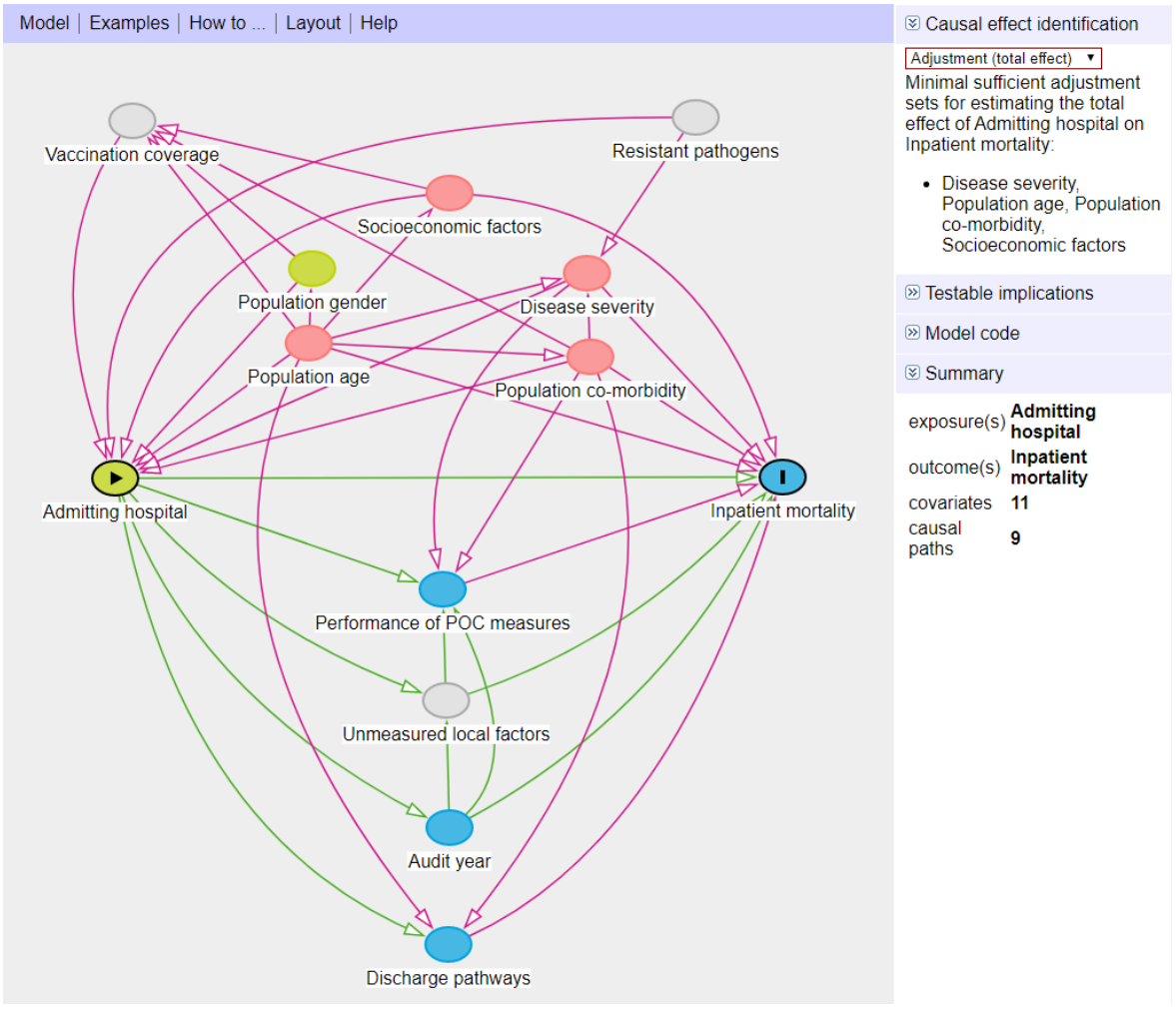


Figure 4.2 - DAG for admitting trust and 30-day readmission

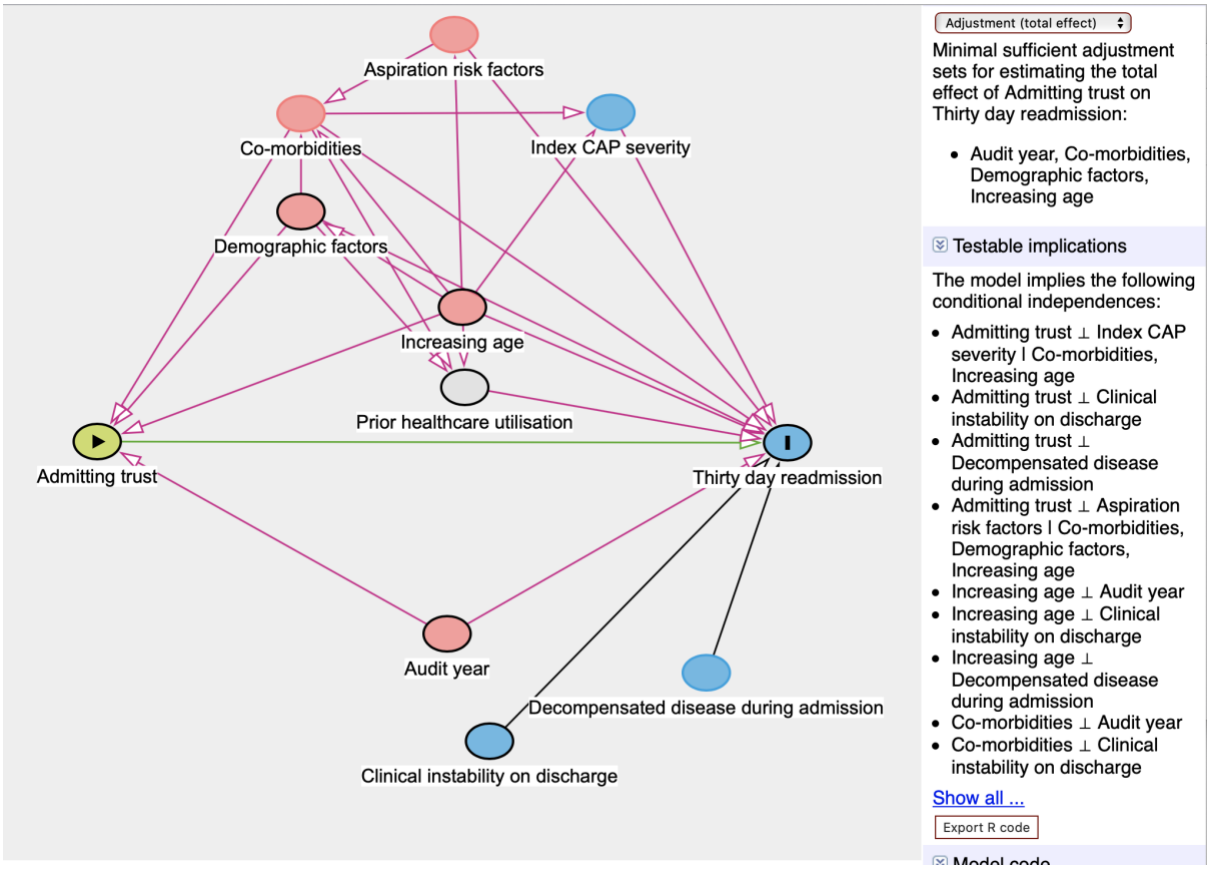
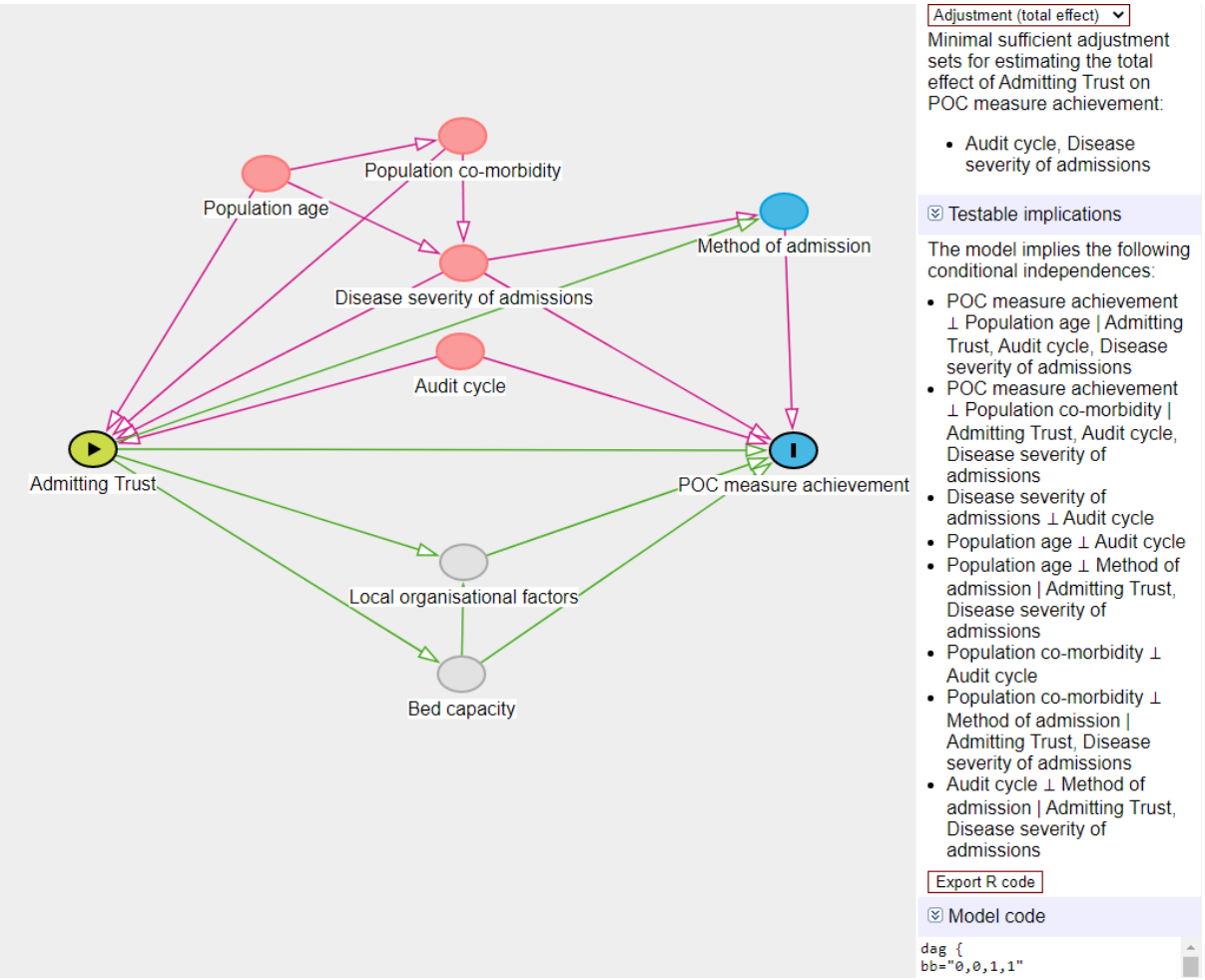


Figure 4.3 - DAG for admitting trust and POC measures



Mixed effects logistic regression models, adjusted for potential confounders clustered by admitting trust, were used to calculate the probability of an outcome for each individual case. The expected number of each outcome per trust was then calculated as the sum of the individual probabilities. The probability of an event occurring in an individual treated at one Trust compared with the probability of the outcome occurring in England across all participating Trusts is derived from the ratio of observed to expected events per trust, multiplied by the whole population rate x100.

Funnel plots for institutional comparison of the primary outcomes were produced according to Spiegelhalter's method for the outcome adjusted for individual case-mix (131). In these plots, the proportion of inpatients with each healthcare outcome at a trust is plotted against the total number of patients at the trust, forming a funnel shape around the outcome. Lines for the 95% (2 standard deviation) and 99.8% (3 standard deviation) confidence limits are superimposed around the average value for the whole cohort. Using these limits, three performance categories are defined: i) category 1 – 'lower than expected' (below or equal to the lower bound of the 95% limit, ii) category 2 – 'normal' (within the 95% limits) and, iii) category 3 – 'higher than expected' (above or equal to the upper bound of the 95% limit).

4.2.5.1 Association between trust mortality outlier status and CAP bundle component performance

Associations between performance of POC measures and outlier status for trust mortality from the primary analysis were tested using univariate logistic regression models. Binary outcome variables were derived from the funnel plots comparing outlying Trusts for healthcare outcomes (eg. those in the 'lower than expected' or 'higher than expected' categories compared to the 'normal' Trusts). Exposure variables were binary POC measures as

described above and the continuous variables median time to antibiotics and CXR at each Trust.

4.2.5.2 Rankability of Outcome Measures

Rankability is described as the proportion of observed variation in a healthcare outcome between providers that is due to true differences rather than chance or natural variation (103, 132). It is displayed as a proportion and interpreted as low (0-50%), moderate (50-75%) or high (>75%) (103, 133). The rankability of the outcome measures were calculated using the following calculation:

$$Rankability = \tau^2/(\tau^2 + \text{median}\sigma^2)$$

In this equation, τ^2 denotes the heterogeneity measured by a random effects logistic regression model (differences between the trusts) and σ^2 the standard error of individual trusts from a fixed effects logistic regression model. Healthcare outcomes assessed were 30-day inpatient mortality, readmission and proportion of cases with short and long LOS at each trust. Estimates of rankability were calculated using both unadjusted logistic regression models and models adjusted for variables as above.

4.2.6 Missing Data

Cases missing data on key variables (healthcare outcomes, POC measures and adjustment variables) were excluded and a restricted complete case analysis was performed. The proportions of missing data for each key variable were examined across the dataset and by trust; the average proportion missing across trusts was calculated. To investigate the effect of missing data, sensitivity analyses were performed using multiple imputation to calculate: i) the adjusted probability of mortality at a trust, and ii) where >5% of data were missing, the estimated proportion of POC measure achievement by trust. These were compared to observed results and differences described using appropriate summary statistics.

4.2.7 Ethics and Communication with outliers

For the 2018/19 national audit, ethical permission for collection of hospital identifiers without consent was granted via a Section 251 application (CAG reference number 18/CAG/0147) and provided by NHS Digital following a DARS application. Hospitals with outlying results were communicated with via the BTS in accordance with their outlier policy.

4.3 Results

4.3.1 BTS aggregated dataset (A) analysis

A total of 34,194 cases over the 6 audit cycles were available for analysis from 151 NHS Trusts. After removal of Trusts with no data entered in the latest audit cycle (winter 18/19) and data from Trusts with <50 cases (4 Trusts, 108 cases), 118 Trusts with 31,712 cases remained for analysis of variation. The proportion of missing data for adjustment variables and healthcare outcomes was low (<5% for each variable) across the whole cohort (Table 1) and by Trust (Table 2). The proportion of cases with missing data on time to first antibiotics and CXR were higher (17.4% and 15.1% respectively) and varied by trust.

Table 4.1 - Proportion of missing adjustment, outcome and process of care data by individual case

Variable	Number missing	Denominator	%
Age	629	31712	1.98
CURB65 score variables:			
Confusion	703	31712	2.22
Urea	424	31712	1.34
RR>30	378	31712	1.19
BP<90	417	31712	1.31
Healthcare Outcomes:			
Inpatient death within 30 days	159	31712	0.50
Length of Stay*	439	26602	1.65
Readmission within 30 days of discharge*	1024	26602	3.85
Critical care admission	559	31712	1.76
POC measures:			
Time to first antibiotic	5534	31712	17.45
Time to CXR	4792	31712	15.11
Guideline concordant antibiotics	1094	31712	3.45
Use of severity score	1266	31712	3.99
Bundle compliance	7706	31712	24.30

**Surviving cohort only examined. For time to first antibiotic and time to CXR, times prior to admission or >72 hours after admission were treated as missing data*

Table 4.2 - Median proportion of missing adjustment, outcome and process of care data by participating trust

Variable missing	Median % missing data across Trusts	IQR %	Range %
Age	0.91	0-2.03	0 - 20.8
CURB65 score variables:			
Confusion	1.17	0.35-2.46	0 – 22.5
Urea	0.32	0-1.06	0 – 21.3
RR>30	0.5	0-1.38	0 – 21.3
BP<90	0.57	0-1.67	0 – 21.7
Outcomes:			
Inpatient death within 30 days	0	0-0.44	0 - 8.5
Length of Stay*	1.45	0.53-2.25	0 – 6.1
Readmission within 30 days of discharge*	1.46	0.75-4.44	0 – 37.9
Critical care admission	0.96	0.47-2.49	0 – 13.8
POC measures:			
Time to first antibiotic	15.4	10.9-22.1	4.13 – 75
Time to CXR	12.9	9.58-19.4	0.69 – 50.8
Guideline concordant antibiotics	2.25	0.94-4.14	0 – 20
Use of severity score	2.48	0.75-6.79	0 – 25

**Surviving cohort only examined. For time to first antibiotic and time to CXR, times prior to admission or >72 hours after admission were treated as missing data*

4.3.2 Healthcare Outcomes

The mean adjusted institutional mortality rate across the 118 participating trusts was 15.9% (SD 4.70) (Table 3). The funnel plot of institutional adjusted mortality rates identified 30 (25.4%) outlying Trusts; 16 (13.6%) were lower than expected and 14 (11.9%) were higher than expected (Figure 4; Table 4). The mean adjusted institutional rates of readmission and critical care admission were 12.7% (SD 3.86) and 6.08% (SD 2.68) respectively. The number of outlying trusts was lower than mortality for both (readmission n=16, 13.6%; critical care admission n=23, 19.5%; Figure 5).

The median LOS was 5 days (IQR 5-6 days). The mean adjusted institutional rate of patients with a LOS of ≤1 day or >10 days was 13.15% (SD 6.04) and 22.8% (SD 6.46) respectively. More outlying Trusts were identified for both; 47 (39.8%) trusts with a LOS≤1 day (‘lower than expected’ n=27, 22.9%; ‘higher than expected’ n=20, 16.9%) and 37 (31.4%) trusts with a LOS>10 days (‘lower than expected’ n=22, 18.6%; ‘higher than expected’ n=15, 12.7%).

Table 4.3 - Outcome measures across the cohort and by Trust

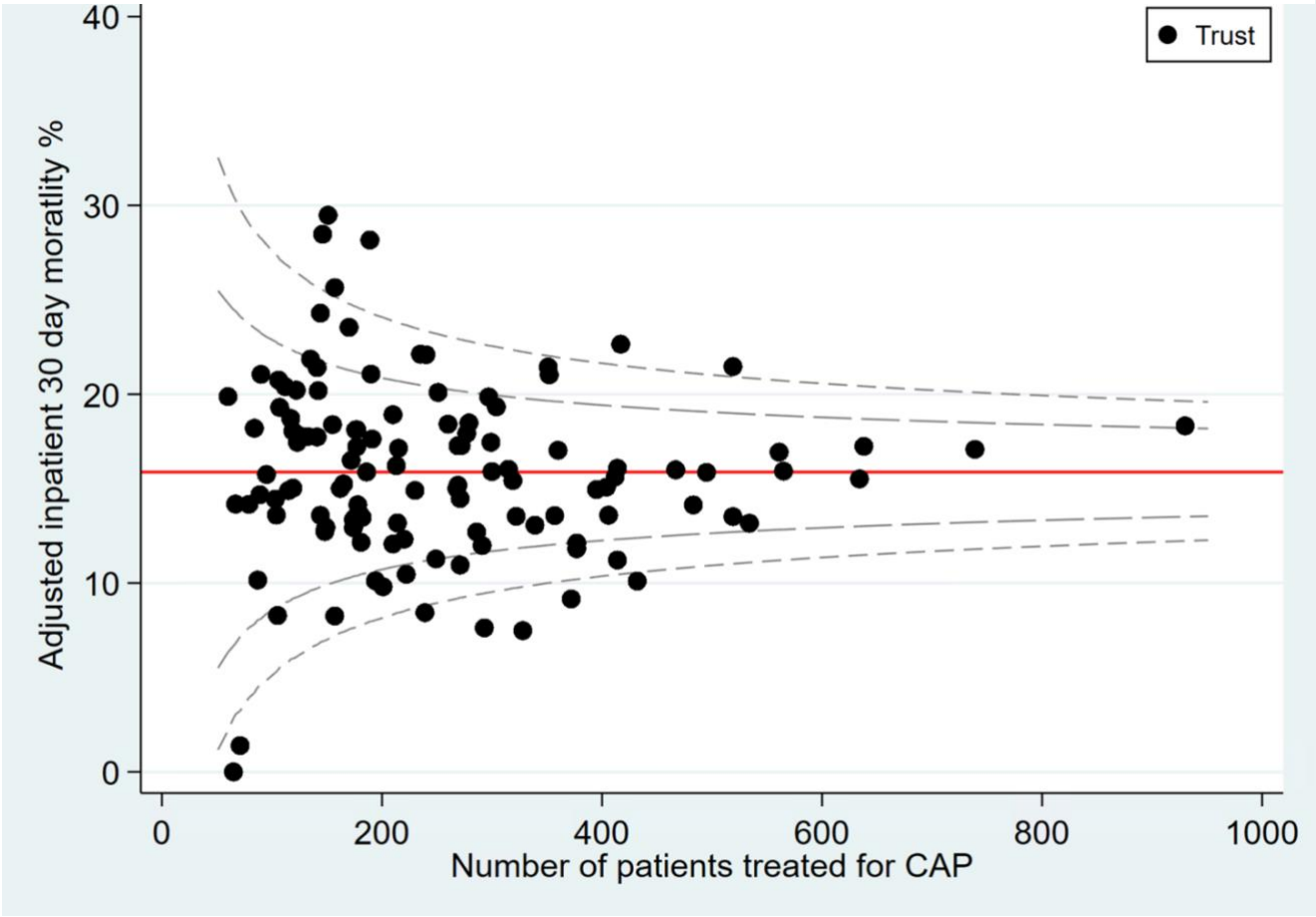
	Cases (n)	Cases with outcome (n, %)	Cases per trust (n)		Unadjusted institutional rate (%)		Adjusted institutional rate (%)	
			Median (IQR)	Range	Mean	Range	Mean	Range
Inpatient death within 30 days	31553	4951 (15.69)	211.5 (144-322)	60-930	15.4 (5.57)	0-35.8	15.9 (4.70)	0-29.5
Readmission within 30 days of discharge	25713	3354 (13.04)	176.5 (110-270)	47-773	12.4 (3.91)	3.45-24.5	12.7 (3.86)	3.59-25.3
Critical care admission	31153	1835 (5.89)	207 (142-323)	60-947	5.65 (2.76)	1.08-19.9	6.08 (2.68)	1.33-16.0
Length of stay (days)			177 (115-273)	47-777	5 (5-6)*	3-10		
Length of stay ≤1 day	26309	3271 (12.43)	177 (115-273)	47-777	12.1 (5.49)	2.33-28.2	13.15 (6.04)	2.79-34.1
Length of stay >10 days	26309	5805 (22.06)	177 (115-273)	47-777	21.6 (6.04)	8.45-46.5	22.5 (6.46)	9.32-47.8

*Median and IQR

Table 4.4 - Outlying trusts (n=118) by healthcare outcome and process of care measures

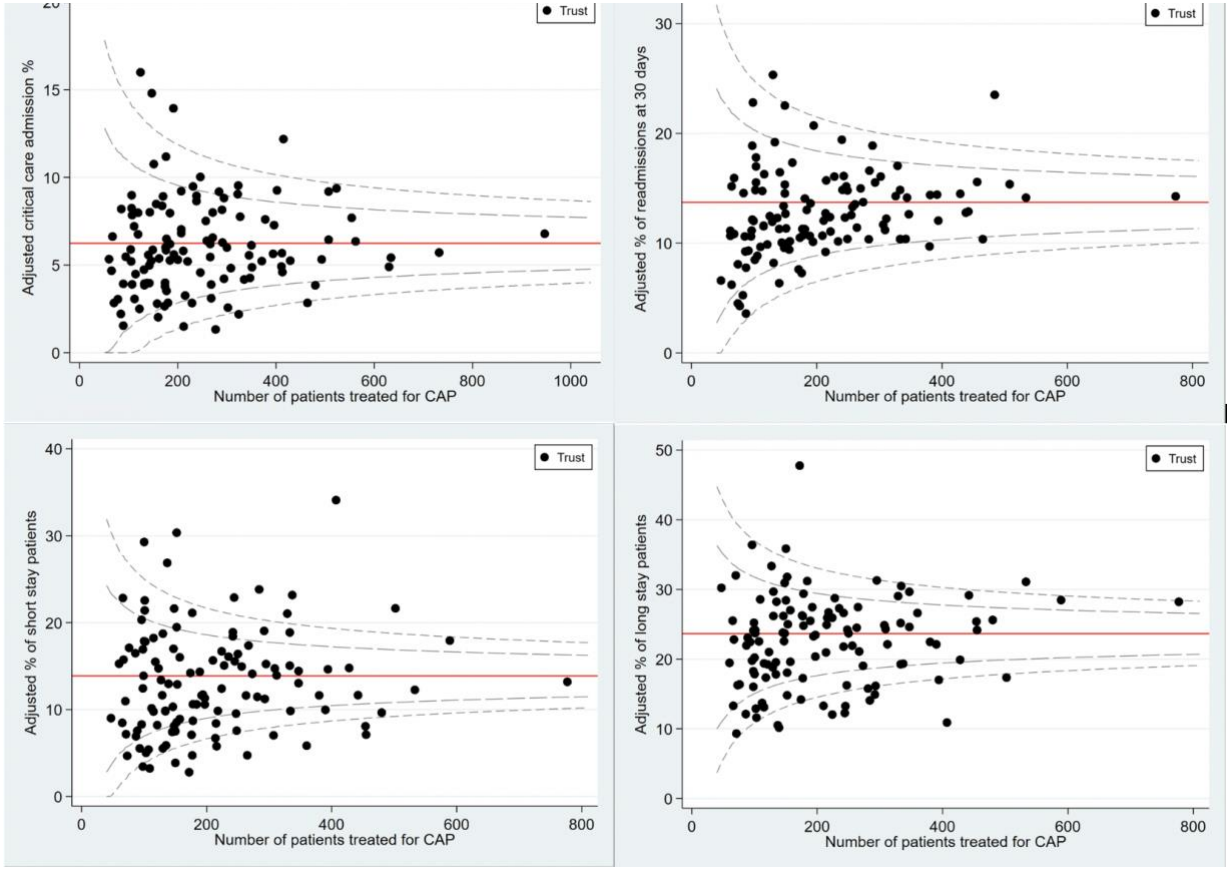
	Trusts within 2 SDs of the mean	**Total number of outliers**	**Trusts under 2SDs from the mean**	**Trusts over 2SDs from the mean**
Outcomes:				
Inpatient death within 30 days	88 (74.6)	30 (25.4)	16 (13.6)	14 (11.9)
Readmission within 30 days of discharge	102 (86.4)	16 (13.6)	9 (7.6)	7 (5.9)
Critical care admission	95 (80.5)	23 (19.5)	9 (7.6)	14 (11.9)
Length of stay <=1 day	71 (60.2)	47 (39.8)	27 (22.9)	20 (16.9)
Length of stay >10 days	81 (68.6)	37 (31.4)	22 (18.6)	15 (12.7)
POC measures:				
Antibiotic received within 4 hours	85 (72.0)	33 (38.8)	12 (10.2)	21 (17.8)
CXR performed within 4 hours	80 (67.8)	38 (32.2)	13 (11.0)	25 (21.2)
Guideline concordant antibiotics	39 (33.4)	79 (66.9)	37 (31.4)	42 (35.6)
Bundle achieved	59 (50.0)	59 (50.0)	26 (22.0)	33 (28.0)

Figure 4.4 - Funnel plot for inter-trust variation in adjusted inpatient mortality at 30 days



Adjusted for fixed effects (age, audit cycle, CURB components and presence of a co-morbidity) and random effects (admitting trust)

Figure 4.5 - Funnel plots for inter-trust variation in adjusted proportion of readmissions, critical care admissions, short and long length of hospital stays (clockwise from top left)



Clockwise from top left: proportion admitted to critical care, readmitted within 30 days of discharge, long and short stay admission. All adjusted for fixed effects (age, audit cycle, CURB components and presence of a co-morbidity) and random effects (admitting trust).

Only 24 (20.3%) trusts were within 2 standard deviations across all five outcome measures examined; the remainder of trusts were in an outlying category at least once (Table 5). One trust was identified with higher than expected mortality and readmission rates. Two trusts had a higher than expected proportion of patients with a LOS≤1 day and readmission rate. There was no association between the proportion of patients with a LOS≤1 day and having higher than expected readmission rates (uOR 0.96, 95% CI 0.83-1.10).

Table 4.5 - Multiple outlier status of trusts

Frequency of outlier status	Outcome Outlier (n, %)	POC Outlier (n, %)
0	24 (20.3)	19 (16.1)
1	51 (43.2)	27 (22.9)
2	28 (23.7)	39 (33.1)
3	14 (11.9)	28 (23.7)
4	1 (0.8)	5 (4.2)

4.3.3 Process of Care Measures

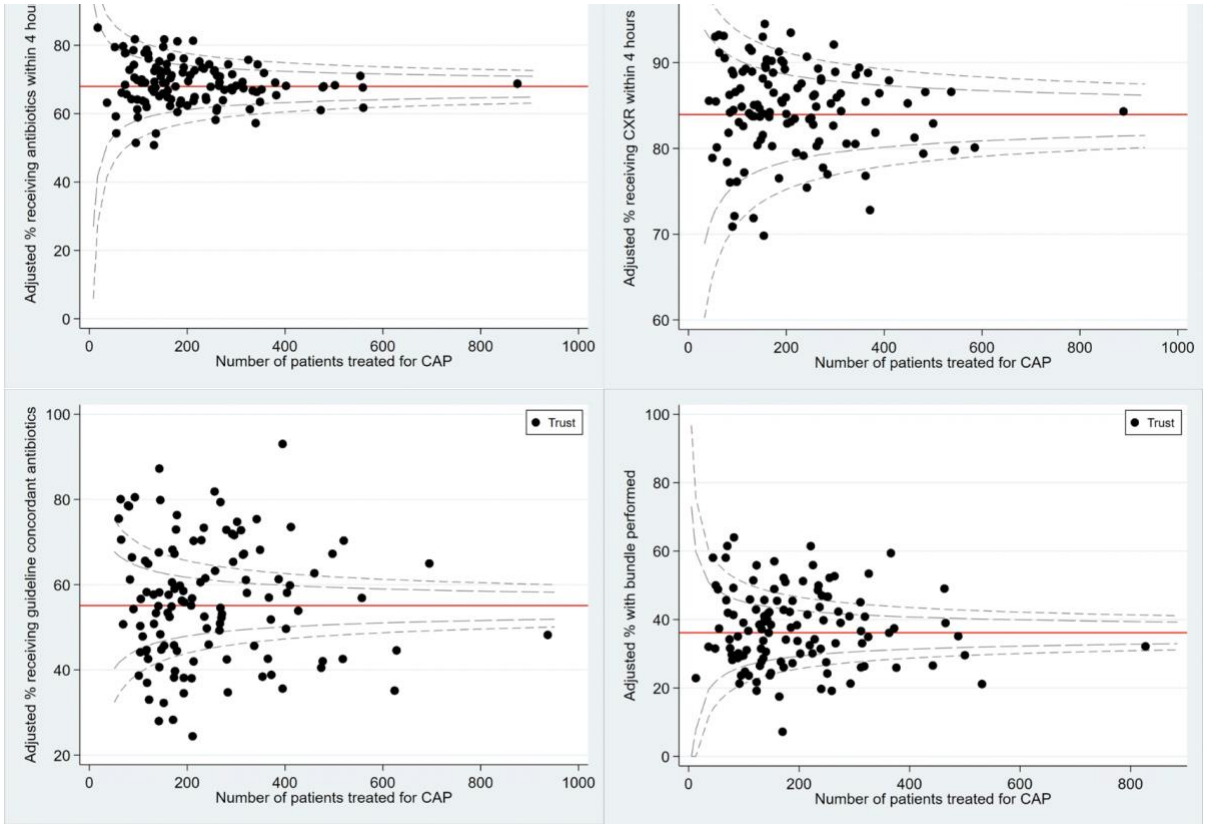
The mean institutional adjusted proportion of patients receiving i) antibiotics and ii) CXR within 4 hours was 68.8% (SD 6.51) and 84.6% (SD 5.14) respectively (Table 6). For all POC measures, more outliers were observed in the 'higher than expected' than the 'lower than expected' group (Table 4). For antibiotics, a funnel plot identified 33 outlying Trusts; 12 'lower than expected' and 21 'higher than expected' (Figure 6; Table 4). For CXR, a funnel plot identified 38 outlying Trusts; 13 'lower than expected' and 25 'higher than expected'. Greater inter-Trust variation was seen in the use of guideline concordant antibiotics and proportion with bundle achieved; 79 (37 'lower than expected', 42 'higher than expected') and 59 (26 'lower than expected', 33 'higher than expected') outlying Trusts were observed respectively.

Nineteen trusts (16.1%) were in within two standard deviations across all process of care measures; five trusts were consistently identified as outliers across all four POC measures.

Table 4.6 - POC measures achieved across the cohort and by Trust

	Cases (n)	Cases per Trust (n)		Cases with achieving POC measure (n, %)	Unadjusted institutional rate (%)		Adjusted institutional rate (%)	
		Median (IQR)	Range		Mean	Range	Mean	Range
Antibiotic received within 4 hours	26178	178 (117-267)	17-875	18040 (68.91)	69.8 (7.19)	49.5-88.2	68.8 (6.51)	50.8-85.1
CXR performed within 4 hours	26920	185 (124-275)	42-889	22867 (84.94)	85.2 (5.19)	70.1-95.5	54.6 (5.14)	69.8-94.5
Guideline concordant antibiotics	30618	208.5 (143-316)	60-937	17448 (56.99)	57.2 (14.5)	26.1-89.5	56.1 (14.2)	24.4-93.0
Use of severity score	30446	210 (139-321)	54-943	13265 (43.57)	42.8 (14.5)	10.8-81.9	44.4 (15.0)	11.8-86.9
Bundle achieved	24006	165.5 (109-250)	13-827	8849 (36.86)	37.3 (11.3)	7.06-67.1	37.3 (11.1)	7.19-64.0

Figure 4.6 - Funnel plots for POC measures.



Clockwise from top left: Funnel plots for inter-trust variation in adjusted proportion of readmissions, critical care admissions, short and long length of hospital stays. *Adjusted for fixed effects (audit cycle, CURB components) and random effect (admitting trust).*

4.3.4 Association between outcome and POC measures

Associations between trust performance of POC measures and the odds of being an outlying Trust were tested with logistic regression models. No POC measures were associated with a trust having a lower than expected mortality (Table 7). The median time to first antibiotic was slightly longer in trusts with higher than expected mortality (2.85 hours vs. 2.61 hours). The odds of a trust having higher than expected mortality increased by nearly 3-fold with each one hour increase in median time to first antibiotic, however this did not reach statistical significance (OR 2.66, 95% CI 0.83-8.50, p=0.10). No other POC measures were associated with a trust having higher than expected mortality.

Table 4.7 - Association between POC measures and trust mortality category

	Within 2 SDs (n=88)	**Mortality lower than expected (n=16)**			**Mortality higher than expected (n=14)**		
	Trust performance (Mean / SD)	Trust performance (Mean / SD)	Odds Ratio	p value	Trust performance (Mean / SD)	Odds Ratio	p value
Median time to first antibiotic (hours)	2.61 (0.51)	2.56 (0.38)	0.83 (0.27-2.50)	0.73	2.85 (0.46)	2.66 (0.83-8.50)	0.1
Antibiotics within 4 hours (%)	69.0 (6.40)	69.5 (7.49)	1.01 (0.93-1.10)	0.77	67.2 (6.27)	0.96 (0.88-1.05)	0.35
Median time to CXR (hours)	1.79 (0.35)	1.68 (0.31)	0.35 (0.66-1.83)	0.21	1.77 (0.22)	0.81 (0.14-4.59)	0.82
CXR within 4 hours (%)	84.5 (5.25)	85.5 (4.93)	1.04 (0.93-1.16)	0.47	84.0 (4.89)	0.98 (0.88-1.09)	0.75
Guideline concordant antibiotics (%)	55.8 (14.5)	53.9 (12.4)	0.99 (0.95-1.03)	0.61	60.4 (13.8)	1.02 (0.98-1.06)	0.27
CAP Bundle achieved (%)	37.5 (11.1)	34.2 (11.3)	0.97 (0.93-1.02)	0.28	40.2 (10.8)	1.02 (0.97-1.08)	0.4

Unadjusted odds ratios for the odds of a Trust having a lower than or higher than expected mortality compared to the baseline group, within 2 standard deviations of the mean, by performance of POC measures

4.3.5 Rankability of healthcare outcomes

The rankability of healthcare outcomes assessed was low (<50%) for each outcome suggesting that a high proportion of the observed variation between trusts is due to natural variation. For inpatient mortality, crude rankability was 34.4% (Table 8). Following adjustment for patient and disease characteristics, rankability decreased to 25.3%. This is interpreted as 25.3% of the observed variation in trust mortality is due to unexplained true differences between trusts. Adjusted rankability for admission to critical care (23.4%), readmission within 30 days (9.0%) and the proportion of patients with short (32.2%) and long stays (28.9%). Ranking hospitals by these outcomes in CAP is therefore unlikely to be valid due to the significant role of natural variation.

Table 4.8 - Rankability of outcome measures

Healthcare outcomes	Unadjusted Rankability (%)	Adjusted Rankability (%)*
Inpatient 30-day mortality	34.4	25.3
Critical care admission	26.1	23.4
Readmission	10.3	9.0
Short stay	29.6	32.2
Long stay	27.3	28.9

**Adjusted for age, audit cycle, binary components of the CURB 65 score (minus age) and presence or absence of a co-morbidity.*

4.3.6 Sub-analysis of the BTS-HES linked Winter 2018/19 dataset

4.3.6.1 Thirty and ninety-day mortality

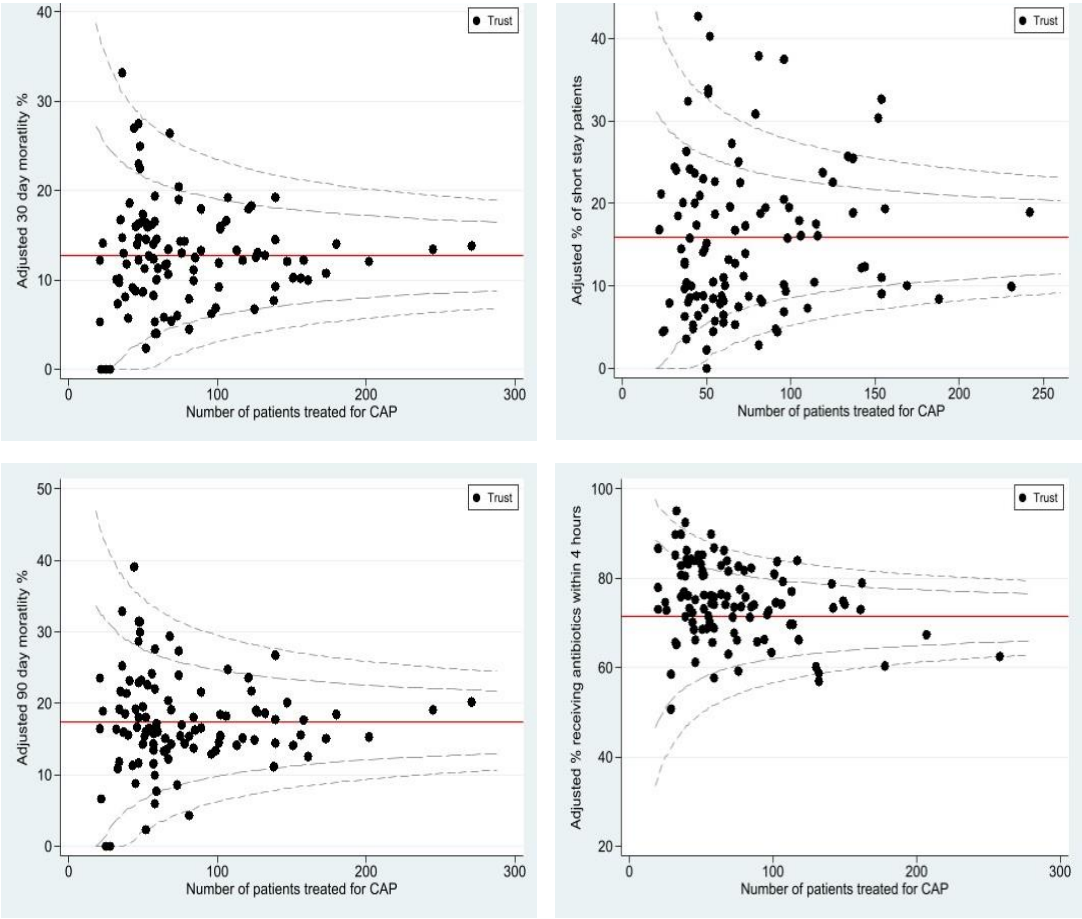
Of 10,196 cases from 122 participating trusts enrolled in the winter 2018/19 audit, 903 cases at 10 trusts in devolved nations were excluded as no HES data were available. Following exclusion of cases missing key adjustment variable data (CURB65 data n=942; IMD n=129), nine trusts (119 cases) with total case numbers of less than 20 were excluded leaving 8120 cases from 103 Trusts for analysis.

Mean adjusted thirty and ninety-day trust mortality rates were 12.5% (SD 6.6) and 17.3% (5.8) respectively (Table 9). For 30-day mortality, a funnel plot identified 15 (14.6%) Trusts as outlying (Figure 4). Of the 5 (4.9%) trusts with lower than expected 30-day mortality, 4 also had lower than expected 90-day mortality however none were identified in the lower mortality group for inpatient mortality at thirty-days in the primary analysis. Of the 10 (9.7%) Trusts with higher than expected mortality, nine also had higher 90-day mortality. Three trusts were consistently identified in the higher than expected mortality group in both analyses.

Table 4.9 - Proportions of outcomes and process of care measures per trust in the winter 2018/19 data sub-analysis

	Number of trusts	Number of cases	Population rate (%)	Median cases per trust (IQR)	Range (%)	Mean unadjusted institutional rate (%)	Range	Mean adjusted institutional rate (%)	Range (%)
Thirty-day mortality	103	8120	1020 (12.6)	60 (47-102)	21-271	12.5 (6.6)	0-38.9	12.7 (5.8)	0-33.2
Ninety-day mortality	103	8120	1400 (17.2)	60 (47-102)	21-271	17.2 (7.6)	0-40.9	17.3 (6.6)	0-39.1
Length of stay ≤1 day	107	8007	1115 (13.9)	60 (43-96)	22-242	13.6 (7.9)	0-36.5	15.3 (9.2)	0-42.7
Antibiotic received within 4 hours	103	7487	5610 (74.9)	59 (43-94)	20-258	76.4 (8.9)	51.7-97.0	74.7 (8.6)	50.7-95.1

Figure 4.7 - Inter-trust variation in outcome measures – winter audit 2018/19



Clockwise from top left: adjusted 30 day-mortality, proportion of short stays^, proportion of patients receiving antibiotics with 4 hours~, adjusted 90-day mortality*. *Adjusted at an individual level for age, binary components of the CURB 65 score (minus age), presence or absence of a co-morbidity and deprivation score and clustered by Trust. ^Adjusted at an individual level for age, binary components of the CURB 65 score (minus age), presence or absence of a co-morbidity and clustered by trust. ~Adjusted at an individual level for binary components of the CURB 65 score only and clustered by trust.*

4.3.6.2 Short stay patients

Following exclusion of cases missing key adjustment variable data, 8,007 surviving cases from 107 Trusts were available for analysis. The mean adjusted proportion of patients with shorts stays at each Trust was 15.3% (SD 9.2); 32 (29.9%) Trusts were identified as outliers (Table 9; Figure 7). Eleven (68.8%) of the 16 lower and 12 (75.0%) of the 16 higher than expected trusts were in the same group in both analyses.

4.3.6.3 Antibiotics within 4 hours

Following exclusion of cases missing key adjustment variable data, 7487 cases from 103 trusts were available for analysis. The mean adjusted proportion of patients receiving antibiotics within 4 hours at each trust was 74.7% (SD 8.6); 34 (33.3%) trusts were identified as outliers (Table 9; Figure 7). The national audit target for antibiotics within 4 hours is 85%; this was achieved by 20 (19.4%) Trusts. Three (37.5%) of 8 lower and 9 (34.6%) of 26 higher than expected trusts were in the same group in both analyses.

4.3.7 Sensitivity Analysis – Missing Data

To assess the effect of missing adjustment variable data on the calculated probability of mortality for an individual treated at a Trust, probabilities calculated in the primary dataset were compared with those calculated from data with imputed adjustment variables. The median difference between probabilities by Trust was small at 0.32 (IQR 0.18-0.53); no Trust probability changed by over 5% (range 0-4.92%).

To investigate the effect of missing data on the proportion of patients receiving antibiotics and a CXR within four hours by trust, the expected proportion of POC achievement using imputed data was compared with that observed using available data at Trust level. The median Trust difference was low for both measures: time to first antibiotics 0.82% (IQR 0.35-1.64%, range 0.01-10.92%) and time to CXR 0.46% (IQR 0.17-0.93%, range 0.01-4.42%). The estimated proportion receiving antibiotics changed by >5% in only three trusts.

4.4 Discussion

4.4.1 Key Findings

The key findings from this analysis are: i) there is inter-Trust variation in observed mortality after adjustment for case-mix (range 0-29.5%, mean 15.9%, SD 4.7), ii) thirty (25.4%) Trusts were identified as outliers after accounting for natural variation, and iii) 74.7% of the observed variation in adjusted mortality is likely due to chance rather than true differences. The extent of observed inter-Trust variation was not consistent across healthcare outcomes; greater variation in hospital stays and less in readmission rates were observed. A high proportion of the observed variation in all outcome measures was due to chance (>67.8%). Regarding POC measures, observed inter-Trust variation in guideline concordant antibiotic use was greater than other measures examined. No significant association between outlier Trust status for mortality and Trust performance in POC measures was observed, however small numbers limit analysis.

4.4.2 Comparison with published literature

Mirroring the findings from the Atlases of variation in respiratory disease, our results describe inter-Trust variation in healthcare outcomes following admission with CAP in the UK that persist following case-mix adjustment (49, 56). Similar inter-hospital variation in mortality following CAP has been demonstrated in comparable healthcare systems (79, 99). Inferences regarding quality of care made from variation in outcomes have been consistently challenged (72, 134). Indeed, our analysis demonstrated low rankability in all outcome measures and suggests a high proportion (>67.8%) of observed variation is due to chance. Low rankability of outcome measures has been demonstrated in other acute medical conditions. *Hofstede et al.* reported low rankability of outcomes in heart failure (HF), acute myocardial infarction (AMI) and stroke (133). They demonstrated improvement using pooled data over longer time periods or

using a composite outcome measure (133). In the Netherlands, the rankability of in-hospital mortality post AMI and readmission following HF admission were moderate at 58% and 51% respectively (103). Taken together, these results do not support the use of ranking Trusts by healthcare outcomes in CAP.

The extent of observed inter-Trust variation was not consistent across healthcare outcomes; in concordance with published evidence to date greater inter-Trust variation in LOS and less variation in readmission rates were observed (135). Length of stay is strongly influenced by multiple factors (patient co-morbidities and wishes, hospital systems and resources, treating physician practice) and this may explain in part the greater variation observed (136, 137). It is not a unidirectional outcome; a long LOS may be appropriate in a severely ill patient treated in critical care but not where system factors prevent discharge in an otherwise medically optimised patient. However, patients with low severity disease in whom community management is appropriate should be managed in the same day setting (1, 18). The marked variation in proportion of short stays at Trusts with no demonstrated link to readmission rates suggests this might be a suitable improvement target. Indeed, the CAP Same Day Emergency Care (SDEC) Commissioning for Quality and Innovation due in 2021 in England aims to improve this (138). Low inter-hospital variation in readmission rates are reported in other acute medical conditions (139). Over the ten years of the national CAP audit, readmission rates increased from 10.5% to 14.3% (17). Limited inter-Trust variation observed in this analysis suggests a national rather than local cause. Notably, this increase is not reflected by national trends in readmission following all cause admission which are unchanged over a similar time period (22).

For POC measures, the greatest variation was observed in the proportion of patients receiving guideline concordant antibiotic therapy. Adherent treatment is key to antimicrobial stewardship and associated with lower

mortality and a decreased time to clinical stability (96, 140-142). CURB65-guided antibiotic therapy has been associated with decreased broad-spectrum antibiotic use without adverse impact on outcomes (143). Non-adherence is due to a mixture of factors: clinical (worse in low disease severity, atypical presentation) and treating physician (guideline unfamiliarity, senior physician influence) (17, 144, 145). Wide variation below the national target suggests improvement strategies are required; a focus on moderate/high severity disease where the mortality benefit will be greatest is warranted.

The mean proportion of patients at a Trust receiving antibiotics within the four hour target was 76.4%, below the 85% national target (17). No significant association between higher than expected mortality at a Trust and achievement of POC measures were observed. It does not follow that targeting improved delivery of POC measures is not valid. Firstly, this analysis is likely underpowered to detect a mortality benefit at Trust level. Given this, the observed non-significant finding that the risk of a Trust having higher than expected mortality increased by nearly 3-fold with each one hour increase in median time antibiotics is noteworthy. At an individual level, timely antibiotic delivery is associated with lower mortality and is a key component of the BTS CAP Care Bundle (39, 77). This highlights the difficultly of correlating quality of care with outcomes at an institutional level due to the complexity of factors affecting any association (72).

4.4.3 Strengths and Limitations

The main strengths of this analysis are: i) the use of a large granular dataset comprising of multiple Trusts, each with representative case numbers, ii) the dataset includes both POC and outcome data linked at a patient level, and iii) a robust statistical methodology allowing for case-mix adjustment and natural variation is utilised. National guidelines for the treatment of CAP have not significantly changed since 2009 allowing pooling of data across audit cycles.

The main limitation is the high proportion of missing data that varies by trust. The quality of the national audit data relies on the accuracy of data entry by participating sites performed by clinicians subject to workload pressures. Sensitivity analyses show minimal change to overall results using imputed data, however outcome estimates at Trusts with a high proportion of missing data or low number of cases are less representative. Identified outlying Trusts should check quality of data entry as the first step in investigating outlier status.

Our study is susceptible to biases inherent in retrospective observational studies, particularly case selection bias. The audit protocol requests cases are selected at random however, case selection bias due to unmeasured local factors cannot be excluded. The audit is open to all Trusts and, of 135 acute non-specialist Trusts in England, 118 are represented in this work. Non-response bias due to differences between participating and non-participating trusts cannot be excluded.

Outcome estimates may be subject to incomplete case-mix adjustment due to lack of data on the severity of co-morbid disease. Adjustment by co-morbidity data, particularly that derived from coded data, is subject to constant risk fallacy due to variation in coding practices between hospitals (124, 146). Our analysis minimises this risk by using clinician verified audit co-morbidity data. The audit dataset captures data only on patients hospitalised with CAP, not those treated in the community. It is therefore sensitive to unmeasured variation in admission thresholds between Trusts.

The audit datasets lack information on the causative pathogen and antimicrobial resistance which could differ between areas; however, major regional differences in the respiratory pathogens associated with CAP and antibiotic resistance patterns are not identified in the UK. The datasets lack data on individual vaccination status. At the time of the audits, vaccination of adults with the 23 valent pneumococcal polysaccharide vaccine (PPV23) and annual vaccination against influenza was recommended for those over

the age of 65 or those in a clinical risk group (66). Coverage with the PPV23 vaccine in those 65 or over is 70% in England but varies by geographical area (64.4% in London to 72.9% in Cheshire and Merseyside) (70). Although effective against invasive pneumococcal disease and pneumococcal pneumonia, PPV23 is not known to be effective against mortality due to all cause pneumonia (147).

Patients with repeat admissions are not excluded from the audit therefore a patient may be included with two separate admissions within a two-month period. These patients may represent a group with recurrent CAP due to a specific underlying pathology. However, given the short time interval of the annual audit, exclusion of cases discharged within 10 days of admission and clinician review of case notes, the number of patients with multiple admissions is likely small with minimal implications on results.

Chapter 5 Impact of social deprivation on clinical outcomes of adults hospitalised with Community Acquired Pneumonia

5.1 Introduction

An association between deprivation and increased mortality from COVID-19 has been widely reported (148). Deprivation has also been associated with an increased incidence of community-acquired pneumonia (CAP), but its association with mortality from CAP has not been adequately studied (3, 149). The BTS national audit dataset 2018/19 linked to Hospital Episode Statistics (HES) data provides patient level data on adults hospitalised with all-cause CAP and their corresponding level of deprivation based on area of residence. The primary objective of this study was to examine associations between deprivation and adverse outcomes following admission to hospital in England with CAP.

5.2 Methods:

Audit data from the winter 2018/19 British Thoracic Society (BTS) national adult CAP audit were linked at a patient level to HES data for the corresponding admission episode. The linked dataset contains detailed demographic, disease and outcome data from clinical and radiologically confirmed cases of CAP from across England.

Deprivation was measured using Index of Multiple Deprivation (IMD) 2010 scores derived from HES (150). Cases were divided from least to most deprived (quintiles 1 to 5) based on the IMD score in their area of residence (based on lower super output area) (Table 5.1) (150).

Adverse outcomes examined were mortality and 30-day readmission. Readmission was defined as an emergency admission to any acute hospital within 30-days of index discharge in surviving cases, excluding readmission within one day of index discharge.

Table 5.1 - IMD Quintiles

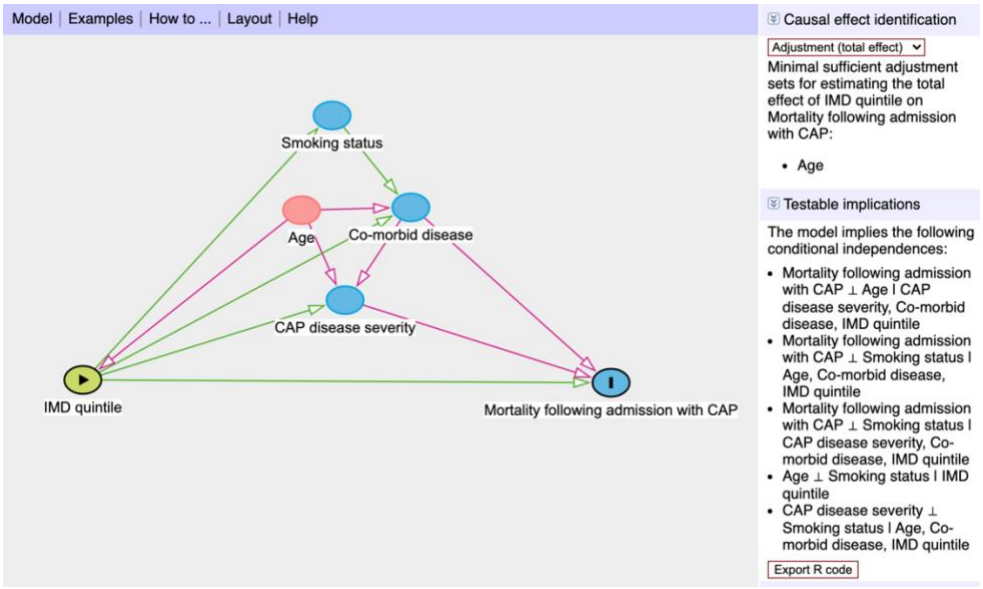
Quintile group	IMD Score range
1	≤8.49 (Least deprived)
2	8.5-3.79
3	13.8-21.35
4	21.36-34.17
5	≥34.18 (Most deprived)

Taken from NPEU Tools, University of Oxford (150)

5.2.1 Statistical Analysis:

Characteristics of the cohort were described using appropriate summary statistics. Multivariable logistic regression models were used to calculate the adjusted odds of all-cause 30-day mortality with increasing deprivation. The minimal adjustment set was identified as age only following review of the literature for potential confounders and production of a Directed Acyclic Graph (http://dagitty.net/) (Fig. 5.1) (130). Age was identified as a potential effect modifier on the effect of IMD quintile on mortality (6). A test for interaction using binary variables (≥65 vs <65 years; IMD quintiles 1-3 vs 4-5) was performed to assess the requirement for stratification by age groups. All analyses were performed using STATA version 16.0.

Figure 5.1 - DAG for deprivation and mortality



5.3 Results

There were 9,165 cases available for analysis following exclusion of 128 cases (1.4%) without IMD scores. The highest proportion of patients were in the most deprived quintile (n=2263, 24.7%; Table 5.2); and they were younger than patients in the least deprived quintile (median age 71 vs 79 years respectively). In persons aged ≥65 years, the age adjusted odds of high severity disease on hospital admission increased with deprivation (p trend = 0.002); the most deprived were 23% more likely to be admitted with high severity disease than the least deprived (aOR 1.23, 95% CI 1.03-1.47).

Table 5.2 - Cohort demographics by IMD Quintile

IMD Quintile	1 (Least deprived) N %	2 N %	3 N %	4 N %	5 (Most deprived) N %	p for trend
Number of cases	1423 (15.5)	1638 (17.9)	1878 (20.5)	1963 (21.4)	2263 (24.7)	
Median age (IQR)	79 (67-87)	78 (65-86)	76 (63-86)	74 (59-84)	71 (57-81)	
Gender (male)	693 (48.7)	776 (47.4)	896 (47.7)	927 (47.3)	1093 (48.3)	0.891
Co-morbidities:						
Cardiac failure	170 (11.9)	173 (10.6)	177 (9.4)	202 (10.3)	218 (9.6)	0.05
Other chronic cardiac disease	423 (29.7)	480 (29.3)	508 (27.1)	506 (25.8)	528 (23.3)	**<0.0001**
Cerebrovascular disease	130 (9.1)	153 (9.3)	165 (8.8)	184 (9.4)	218 (9.6)	0.59
Liver disease	11 (0.8)	16 (1.0)	30 (1.6)	36 (1.8)	43 (1.9)	**0.0008**
Chronic kidney disease	153 (10.8)	153 (9.3)	206 (11.0)	202 (10.3)	180 (8.0)	**0.02**
Malignancy	121 (8.5)	126 (7.7)	134 (7.1)	154 (7.8)	170 (7.5)	0.43
COPD	259 (18.2)	351 (21.4)	426 (22.7)	517 (26.3)	785 (34.7)	**<0.0001**
Other chronic lung disease	257 (18.1)	251 (15.3)	295 (15.7)	338 (17.2)	359 (15.9)	0.45
Diabetes	204 (14.3)	268 (16.4)	343 (18.3)	357 (18.2)	455 (20.1)	**<0.0001**
Dementia	168 (11.8)	167 (10.2)	201 (10.7)	229 (11.7)	226 (10.0)	0.35
BMI $\geq$ 40	11 (0.8)	13 (0.8)	13 (0.7)	28 (1.4)	35 (1.5)	**0.003**
Severity:						
Mild	549 (38.6)	656 (40.0)	745 (39.7)	793 (40.4)	1021 (45.1)	
Moderate	420 (29.5)	485 (29.6)	531 (28.3)	538 (27.4)	563 (24.9)	
Severe	347 (24.4)	382 (23.3)	433 (23.1)	435 (22.2)	467 (20.6)	**<0.0001***

Not known	107 (7.5)	115 (7.0)	169 (9.0)	197 (10.0)	212 (9.4)	
High severity disease in persons ≥65 years						
N (%)	342/1015 (33.7)	374/1151 (32.5)	427/1249(34.2)	416/1183(35.2)	444/1274 (34.9)	2003/5872 (34.1)
Age adjusted OR (95% CI)	1	0.97 (0.81-1.17)	1.07 (0.89-1.28)	1.17 (0.98-1.40)	1.23 (1.03-1.47)	**0.002**

**Not for trend – denotes association between the variables*

5.3.1 Mortality

Thirty-day mortality was highest in the least deprived quintile (16.8%) and lowest in quintile two (11.6%) (Table 5.3). After adjustment for age, no significant trend between deprivation and mortality was observed (p trend = 0.38). There was effect modification between age and IMD score on mortality (p-interaction 0.03). In those ≥65 years, no association between increasing deprivation and mortality was observed (p-trend = 0.23). In those <65 years, age-adjusted mortality increased with deprivation (p-trend = 0.04). People in the most deprived quintile were 83% more likely to die within 30-days than the least deprived (aOR 1.83, 95% CI 0.84-4.0).

Table 5.3 - Association between deprivation and mortality in the whole cohort and stratified by age group

Quintile	1 (Least deprived)	2	3	4	5 (Most deprived)	p for trend
Whole cohort (all ages)						
Number of cases	1423	1638	1878	1963	2263	
N (%)	239 (16.8)	190 (11.6)	233 (12.4)	235 (12.0)	286 (12.6)	
OR (95% CI)	1	0.65 (0.53-0.80	0.7 (0.58-0.85)	0.67 (0.55-0.82)	0.72 (0.59-0.86)	**0.008**
Age adjusted OR (95% CI)	1	0.66 (0.54-0.82)	0.76 (0.62-0.92)	0.81 (0.66-0.99)	0.98 (0.81-1.19)	0.38
Age <65 years						
Number of cases	316	393	498	645	848	
N (%)	8 (2.5)	11 (2.8)	14 (2.8)	27 (4.2)	37 (4.4)	
OR (95% CI)	1	1.11 (0.44-2.79)	1.11(0.46-2.69)	1.68 (0.75-3.75)	1.76 (0.81-3.82)	**0.04**
Age adjusted OR (95% CI)	1	1.13 (0.45-2.85)	1.16 (0.48-2.80)	1.74 (0.78-3.88)	1.83 (0.84-4.0)	**0.04**
Age ≥65 years						
Number of cases	1107	1245	1380	1318	1415	
N (%)	231 (20.9)	179 (14.4)	219 (15.9)	208 (15.8)	249 (17.6)	
OR (95% CI)	1	0.64 (0.51-0.79)	0.72 (0.58-0.89)	0.71 (0.58-0.87)	0.81 (0.66-0.99)	0.23
Age adjusted OR (95% CI)	1	0.65 (0.52-0.81)	0.74 (0.60-0.91)	0.77 (0.63-0.95)	0.95 (0.77-1.16)	0.70

Baseline group for all analysis is Quintile 1 – the least deprived quintile

5.3.2 Readmission

Data on readmission within 30-days of discharge were available on 8212 cases surviving index admission. The proportion of readmissions was highest in the most deprived quintile (17.1% vs 14.1% in quintile 1) (Table 5.4). Age-adjusted odds of readmission were highest in the most deprived compared to the least deprived (aOR 1.41, 95% CI 1.16-1.73) (p-trend 0.003).

Table 5.4 - Association between deprivation and readmission

	Quintile 1 (Least Deprived)	Quintile 2	Quintile 3	Quintile 4	Quintile 5 (Most Deprived)	p value for trend
Number of cases	1423	1638	1878	1963	2263	
IMD Quintile	1	2	3	4	5	P for trend
N (%)	173 (14.1)	243 (16.4)	261 (15.5)	270 (15.2)	347 (17.1)	
OR (95% CI)	1	1.19 (0.96-1.47)	1.11 (0.90-1.38)	1.09 (0.89-1.34)	1.26 (1.03-1.53)	0.1
Age adjusted OR (95% CI)*	1	1.21 (0.98-1.49)	1.21 (0.98-1.49)	1.17 (0.95-1.45)	1.41 (1.16-1.73)	**0.003**

Baseline group for all analysis is Quintile 1 – the least deprived quintile
**Adjusted for age only.*

5.4 Discussion

In adults hospitalised with CAP, we found that greater social deprivation was associated with increased 30-day mortality in persons aged <65 years, but not in older adults. Regardless of age, increasing deprivation was associated with increasing risk of hospital readmission.

5.4.1 Comparison with literature

Consistent with our findings, an ecological study examining mortality due to respiratory infections in the West Midlands, UK reported the mortality risk in the most deprived was highest in those aged 45-64 years (RR = 4.4) (151). An attenuation of the effect of socio-economic factors on mortality in older populations has been described previously but the mechanism for this effect is unclear (152). Age dependent inequalities in smoking, alcohol use and housing tenure have been implicated (152) Inequalities due to deprivation may be less important than differences in frailty, co-morbidity and social support in older age groups (6). Additionally, the IMD score may not adequately reflect individual socio-economic circumstances of adults residing in care homes, who make up a higher proportion of our older cohort. Potential explanations for an association between deprivation with all-cause hospital readmission include differences in nutrition, air pollution and access to healthcare (153).

5.4.2 Strengths and Limitations

The main strength of this study is the use of a large unique dataset of clinician-confirmed CAP derived from linkage of BTS audit and HES datasets containing patient level data on deprivation, severity and disease outcomes. Selection bias is minimised by the use of routinely collected

audit data. Inclusion of only hospitalised cases might attenuate differences in healthcare seeking behaviours contributing to variation in healthcare outcomes due to deprivation. Misclassification bias cannot be excluded as IMD score is based on area of residence; this may not fully reflect individual patient circumstances . Unmeasured factors associated with deprivation, such lifestyle factors and vaccination status, were not available.

The COVID-19 pandemic has highlighted established health inequalities and led to a recognised need for public health strategies to combat adverse outcomes in deprived areas (154). Our analysis demonstrates adverse outcomes associated with deprivation are also present in all-cause CAP. Strategies to decrease health inequalities associated with deprivation should focus on reducing both index-admission mortality and subsequent readmission related to all acute severe respiratory infections, including COVID-19.

Chapter 6 **Admission to hospital in the UK at a weekend does not influence the prognosis of adults with Community Acquired Pneumonia**

6.1 Introduction

The ‘weekend’ effect, namely an increased risk of mortality in patients admitted on a Saturday or Sunday compared to a weekday, has garnered attention for over a decade. First recognised in Canada in 2001, studies since both in the UK and worldwide have provided evidence for the weekend effect in differing healthcare systems, although the causes remain unclear.(155-157) Most studies rely on retrospective analysis of administrative databases that lack key information such as case severity and admission time by minute, hampering case-mix adjustment and a clear definition of ‘the weekend’ by time. Studies using proxy markers of severity such as blood test results and Early Warning Scores (EWS) within twenty-four hours of admission have suggested that the weekend effect can be attenuated by taking these markers into account.(158, 159)

In the UK, studies on the weekend effect were used as the main driver of government policy for seven-day NHS services. Evidence for a correlation between intensity of specialist hospital staffing and weekend mortality is, however, lacking. The increased mortality risk applies to new admissions only, not all hospital in-patients over the weekend, an effect that would not be expected if increased mortality were due lower staffing intensity alone.(160) In addition, a cross-sectional study of 127 acute hospital trusts in England found no association between Sunday to Wednesday specialist intensity ratios and weekend to weekday mortality ratios.(161)

Unlike some acute emergency conditions that require rapid access to specialist services, the optimal management of CAP, as described in guideline recommendations, can be delivered by acute medical staff of varying grades.(1, 18) As such, clinical outcomes are not expected to be influenced by weekend admission. Our aim was to assess whether outcomes and processes of care for CAP differ between adults admitted at the weekend compared to the weekday.

6.2 Methods

6.2.1 Details of the cohort

Aggregate data from six BTS national adult CAP audits (December and January 2009/10, 2010/11, 2011/12, 2012/13, 2014/15, 2018/19) were used (162). Cases were identified by participating institutions via ICD10 codes mapping to a primary discharge diagnosis of pneumonia (J12.0-J18.0) and selected for eligibility against inclusion criteria to confirm a clinical and radiographic diagnosis of CAP. The audit defines a case of CAP as an immunocompetent adult (≥16 years) hospitalised with symptoms of a lower respiratory tract infection, treated for CAP by the admitting clinicians with accompanying acute infiltrates consistent with pneumonia on admission CXR. The primary outcome of interest was 30-day inpatient mortality. Secondary outcomes included: seven and three-day inpatient mortality, length of hospital stay in days (LOS), critical care admission and readmission within 30-days of discharge. Process of care measures analysed were: CXR and receipt of antibiotics within four hours of admission; use of guideline concordant antibiotics and time to senior review.

6.2.2 Definition of the weekend group

The cohort was divided into two groups based on time and date of first presentation to hospital. Definitions for out-of-hours are taken from the NHS services website: weekday was defined as 08:00 Monday to 18:29 Friday; weekend was defined as 18:30 Friday to 07:59 Monday.(163) Patients admitted on a holiday (defined as 18:30 on the day prior to 07:59 on the next working day) were included in the weekend group.

6.2.3 Statistical Analysis

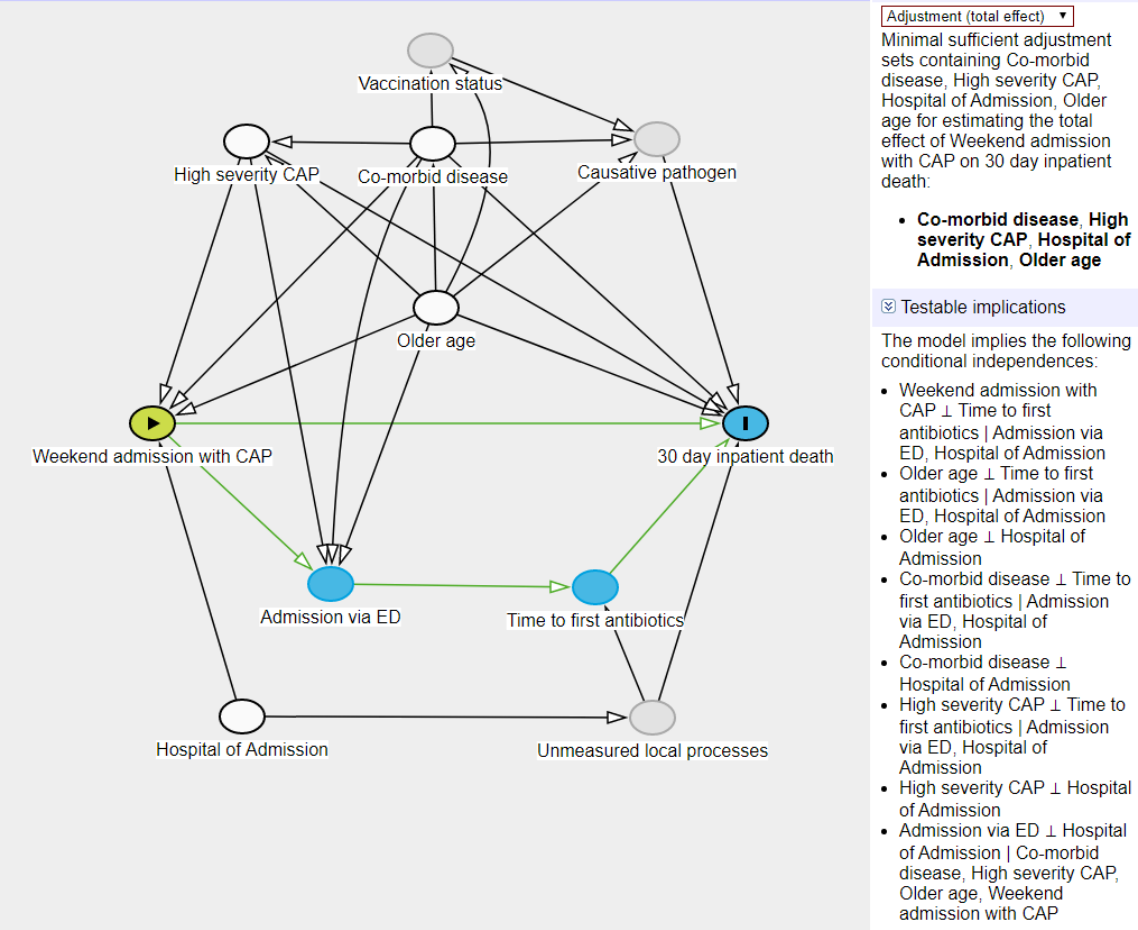
Descriptive statistics were used for group comparison and adjusted odds ratios calculated using a mixed-effects multivariate logistic regression model for each outcome variable. Following review of published literature, minimum sufficient adjustment variable sets were defined using Directed Acyclic Graphs (DAGs) on www.dagitty.net.(164) (Figure 6.1 & 6.2) The adjustment set for mortality included: age, binary variables included in the CURB65 score (excluding age >65) and presence or absence of co-morbidities (congestive cardiac failure (CCF), other chronic heart disease, cerebrovascular disease, liver disease, chronic kidney disease (CKD), malignancy, chronic obstructive pulmonary disease (COPD), other chronic lung diseases, dementia and diabetes). Age groups was included as a continuous variable following a likelihood ratio test to determine best fit. Hospital site of admission was included in the model as a random effect to control for unmeasured local differences in practice and patient populations. A sub-analysis by CURB65 severity category across outcomes was performed using a multivariate logistic regression model adjusted for age and presence or absence of co-morbid disease only.

Analysis of LOS was performed in two ways. Firstly, by generating a binary variable derived from the median LOS for the whole surviving cohort (five days). Patients were censored if they died as an inpatient or if LOS exceeded 90 days. Secondly, using a competing risks analysis to

obtain a hazards ratio for discharge within 30 days. Inpatient death was treated as a competing event. Patients who remained an inpatient at 30 days were censored from the analysis at this time point.

Cases were excluded from all analyses if the time of admission, primary outcome or variables within the minimal adjustment set were missing (<7% of data from each variable). All statistical analyses were performed using STATA 15©.

Figure 6.1 - DAG for weekend admission and inpatient death



Directed Acyclic Graph produced using www.dagitty.net for the exposure 'weekend admission with CAP' and outcome 'inpatient death'. Within the diagram, variables are represented as nodes with arrows to represent causal effects between nodes. Variables included in the minimal adjustment set are shown in white; the minimum adjustment set is identified as age, co-morbidities, disease severity and hospital of admission. Nodes are depicted by the following colours: ancestor of the exposure (green), ancestor of the outcome (blue), ancestor of both exposure and outcome (red), an unobserved variable (grey) and variables adjusted for (white). Causal paths are represented by green arrows, potentially biasing paths are represented by red arrows.

Figure 6.2 - DAG for weekend admission and POC measures

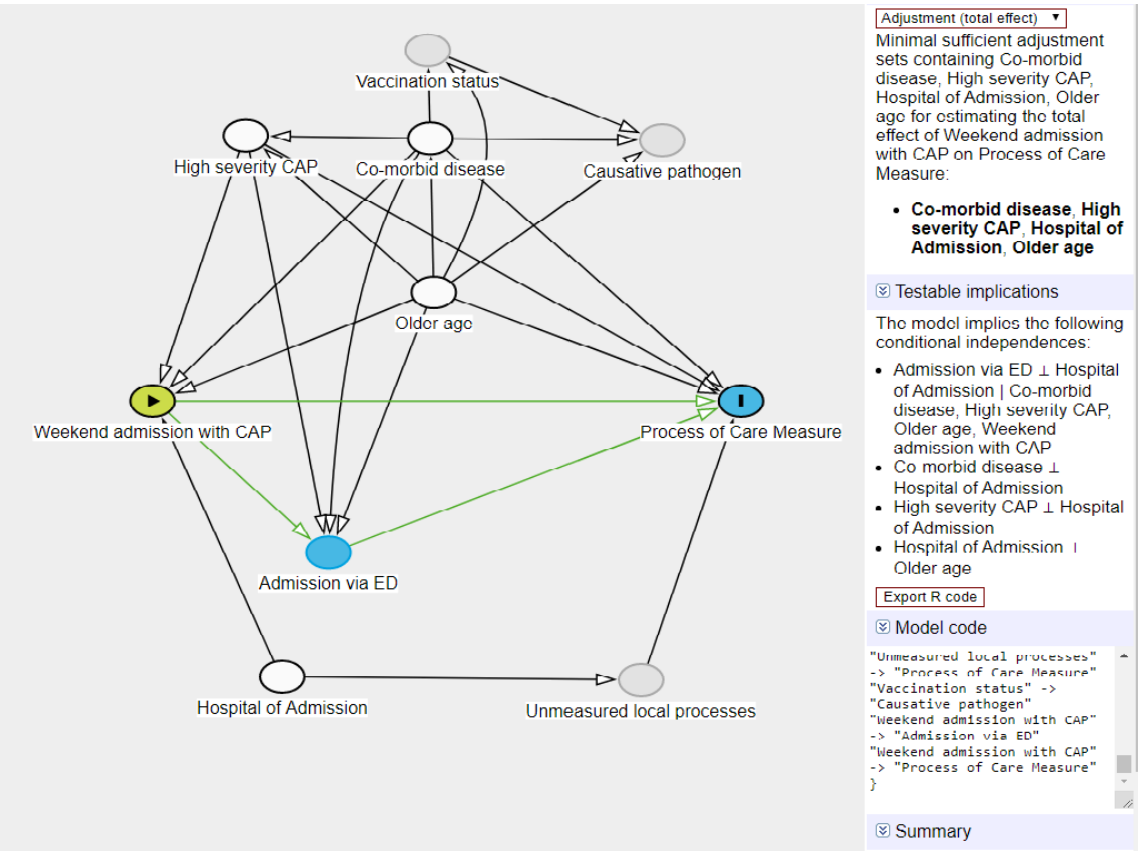


Figure 6.2 - Directed Acyclic Graph produced using www.dagitty.net for the exposure 'weekend admission with CAP' and outcome 'process of care measure in CAP'. Within the diagram, variables are represented as nodes with arrows to represent causal effects between nodes. The minimum adjustment set is identified as age, co-morbidities, disease severity and hospital of admission. Nodes are depicted by the following colours: ancestor of the exposure (green), ancestor of the outcome (blue), ancestor of both exposure and outcome (red), an unobserved variable (grey) and variables adjusted for (white). Causal paths are represented by green arrows, potentially biasing paths are represented by red arrows.

6.3 Results

6.3.1 Characteristics of the cohort

Of 34,194 cases, those missing key data (admission time (n=1008), status on discharge (n=193), age (n=683)) were excluded leaving 32,948 for descriptive analysis. Patients who presented at the weekend (40.7%) were older (72 vs 71.3 years; OR 1.002, 95% CI 1.000-1.003) (Table 6.1), more likely to reside in a care home (14.8% vs 12.8%; OR 1.13, 95% CI 1.06-1.21), be admitted via the emergency department (84.8% vs 73.2%; OR 2.04, 95% CI 1.93-2.16) and have high severity pneumonia than those admitted during weekdays (severe disease 28.9% vs 27.1%; p value for trend 0.003). The weekend group were more likely to have cerebrovascular disease (10.4% vs 9.5%; OR 1.11, 95% CI 1.03-1.19) and dementia (9.2% vs 8%; OR 1.16, 95% CI 1.08-26); but less likely to have chronic kidney disease (7.5% vs 8.9%; OR 0.83, 95% CI 0.77-0.9) or malignancy (7.1% vs 7.7%; OR 0.92, 95% CI 0.84-1.0) (Table 6.1).

Table 6.1 - Population characteristics by cohort group – weekday vs weekend admissions

	Weekday admissions N (%)	**Weekend admissions N (%)**	**Unadjusted OR**	**95% Confidence Interval**	**p Value**
Number of patients	19552 (59.2)	13432 (40.7%)			
Demographics					
Mean age (years)	71.3	72	1.002	1.000-1.003	**0.001**
Gender (male)	9353 (47.8)	6506 (48.4)	1.02	0.98-1.07	0.28
Usual residence care home	12.8	14.8	1.13	1.06-1.21	**0.0002**
Severity by CURB65 category:					
Low (Score 0-1)	8017 (43.0)	5333 (41.7)	1		
Moderate (Score 2)	5558 (29.9)	3753 (29.4)	1.02	0.96-1.07	
High (Score 3-5)	5053 (27.1)	3686 (28.9)	1.1	1.04-1.16	**0.003** (trend)
Admitted via ED	14012 (73.2)	11146 (84.8)	2.04	1.93-2.16	**<0.0001**
Admitted overnight	6431 (32.9)	6947 (51.7)	2.19	2.09-2.29	**<0.0001**
Co-morbidity present:					
Cardiac failure	1726 (8.8)	1179 (8.8)	1	0.92-1.08	0.95
Other chronic heart disease (excluding hypertension)	4578 (23.4)	3112 (23.2)	0.99	0.94-1.04	0.57
Cerebrovascular disease	1853 (9.5)	1398 (10.4)	1.11	1.03-1.19	**0.005**
Liver Disease	236 (1.2)	160 (1.2)	0.98	0.8-1.2	0.83
Chronic Kidney Disease	1741 (8.9)	1007 (7.5)	0.83	0.77-0.9	**<0.0001**
Malignancy	1503 (7.7)	948 (7.1)	0.92	0.84-1.0	**0.04**
Chronic Obstructive Pulmonary Disease	4626 (23.7)	3053 (22.7)	0.95	0.9-1.0	**0.05**

Other chronic lung disease	2667 (13.7)	1752 (13.0)	0.95	0.88-1.01	0.89
Diabetes	2392 (12.2)	1738 (12.9)	1.07	1.00-1.14	**0.06**
Dementia	1557 (8.0)	1229 (9.2)	1.16	1.08-1.26	**0.02**

Table 6.1 - Population characteristics and outcomes by cohort group – weekday vs. weekend admissions. Unadjusted odds ratios (OR) presented with 95% CI and p value.

6.3.2 Healthcare Outcomes

Of 31,400 cases with available data for multivariate analysis of the primary outcome, adjusted mortality in the weekend group was slightly lower at thirty-days (15.4% vs 15.5%; aOR 0.94, 95%CI 0.88-1.01) and seven-days (10.3% vs 10.4%; aOR 0.95, 95%CI 0.87-1.03) but equal at three-days (6.2% vs 6.2%; aOR 0.96, 95%CI 0.87-1.06) (Table 6.2). No differences were found in rates of critical care admission (6% vs 5.8%; aOR 1.05, 95%CI 0.95-1.16) or re-admission within thirty-days of discharge (11.7% vs 11.8%; aOR 0.99, 95%CI 0.92-1.07). Competing risks analysis showed patients admitted at the weekend had a 2% higher probability of discharge at any point from admission to 30 days than the weekday group (aHR 1.02 95%CI 1.00-1.05, p=0.05). When using a binary variable for LOS, patients who survived to discharge and admitted at the weekend were 21% more likely to be discharged within 5 days (55.1% vs 51.0% aOR 1.21 95% CI 1.15-1.28, p<0.0001) but 16% less likely to be discharged within 1 day (11.3% vs 13.3% aOR 0.84 95% CI 0.77-0.90, p <0.0001).

Table 6.2 - Comparison of healthcare outcomes and process of care measures between the weekend and weekday group

	Weekday admissions N (%)	**Weekend admissions N (%)**	**Odds Ratio (95% CI)**	**Adjusted OR* (95% CI)**	**p value**
Outcomes:					
Inpatient death within 30 days	3037 (15.5)	2062 (15.4)	0.99 (0.93-1.05)	0.94 (0.88-1.01)	0.08
Inpatient death within 7 days	2027 (10.4)	1380 (10.3)	0.99 (0.92-1.06)	0.95 (0.87-1.03)	0.19
Inpatient death within 3 days	1210 (6.2)	835 (6.2)	1 (0.92-1.10)	0.96 (0.87-1.06)	0.41
Median LOS (IQR)	5 (3-9)	5 (3-10)			0.23
LOS ≤5 days	8196 (51.0)	6094 (55.1)	1.18 (1.12-1.24)	1.21 (1.15-1.28)	**<0.0001**
LOS≤1 days	2139 (13.3)	1254 (11.3)	0.83 (0.77-0.90)	0.84 (0.77-0.91)	**<0.0001**
Critical care admission	1110 (5.8)	789 (6.0)	1.04 (0.95-1.14)	1.05 (0.95-1.16)	0.32
Readmission within 30 days of discharge	2054 (13.1)	1402 (12.9)	0.99 (0.92-1.06)	0.99 (0.92-1.07)	0.89
Process of care measures:					
Senior review within 12 hours	10322 (57.5)	6206 (50.6)	0.76 (0.72-0.79)	0.74 (0.70-0.77)	**<0.0001**
CXR within 4 hours	15544 (86.0)	10763 (85.9)	0.99 (0.93-1.06)	1.01 (0.94-1.08)	0.77
Antibiotics within 4 hours	11713 (68.7)	8296 (70.3)	1.08 (1.02-1.13)	1.07 (1.01-1.12)	**0.02**
Guideline concordant antibiotics:	10740 (57.0)	7480 (57.6)	1.03 (0.98-1.07)	0.99 (0.94-1.04)	0.80

Table 6.2 – Unadjusted and Adjusted Odds ratios with 95% confidence intervals and p values for outcomes and process of care measures between weekday and weekend admission groups. LOS = length of stay.

*The baseline group for comparison is the weekday admission group. *All outcomes are adjusted for Age, CURB65 score constituents (except age), cardiac failure, other chronic heart disease (excluding hypertension), cerebrovascular disease, liver disease, chronic kideney disease, maligancy, copd, other chronic lung disease, diabetes, dementia and hospital of admission.*

6.3.3 Process of Care Measures

Patients admitted at weekends were more likely to receive antibiotics within four hours (70.3% vs 68.7%; aOR 1.07, 95%CI 1.01-1.12), but less likely to be reviewed by a senior clinician within twelve hours of admission (50.6% vs 57.4%; aOR 0.74, 95%CI 0.70-0.77). There were no differences in performance of CXR within four hours (85.9% vs 86%; aOR 1.01, 95% CI 0.94-1.08) or use of guideline concordant antibiotics (57.6% vs 57%; aOR 0.99, 95% CI 0.94-1.04) (Table 2).

6.3.4 Outcomes by severity category

When sub-divided by CURB65 category, results for each outcome and process of care measure were similar to the analysis of the whole cohort (Table 6.3). For inpatient 30-day mortality, patients with severe disease admitted at the weekend were 9% less likely to die (aOR 0.91; 95%CI 0.83-1.00, p=0.04); no difference was observed in the mild and moderate categories. A slightly lower risk of mortality at 7 and 3 days was also observed (7 days; aOR 0.91 95% CI 0.82-1.00: 3 days; aOR 0.88 95% CI 0.77-0.99). Only weekend admissions with mild disease were less likely to be discharged in one day or less (aOR 0.8; 95%CI 0.72-0.88, p<0.0001). Patients with moderate or severe disease were more likely to receive antibiotics within four hours of admission (moderate aOR 1.13; 95%CI 1.03-1.24, p=0.01; severe aOR 1.14 95%CI 1.02-1.26, p=0.02); no difference was observed in mild disease (aOR 1.01 95% CI 0.93-1.09). No other differences were observed across severity categories for other outcomes or process of care measures.

Table 6.3 - Subgroup analysis by severity category

	Mild (n=13350)		**Moderate (n=9311)**		**Severe (n=8739)**	
	aOR 95% CI	p value	aOR 95% CI	p value	aOR 95% CI	p value
Outcomes:						
Inpatient death within 30 days (%)	0.85 (0.72-1.00)	0.05	1.02 (0.91-1.15)	0.69	0.91 (0.83 - 1.00)	0.04
Inpatient death within 7 days	0.87 (0.71-1.07)	0.19	1.03 (0.89-1.19)	0.64	0.91 (0.82-1.00)	0.06
Inpatient death within 3 days	1.05 (0.80-1.37)	0.73	1.07 (0.89-1.29)	0.44	0.88 (0.77-0.99)	0.04
LOS ≤5 days	1.15 (1.06-1.24)	<0.0001	1.18 (1.07-1.29)	<0.0001	1.42 (1.27-1.58)	<0.0001
LOS≤1 days	0.8 (0.72-0.88)	<0.0001	0.86 (0.73-1.01)	0.07	1.08 (0.85-1.38)	0.53
Critical care admission	1.11 (0.93-1.31)	0.23	1.01 (0.83-1.22)	0.94	1.02 (0.87-1.19)	0.83
Readmission within 30 days of discharge	1 (0.89-1.13)	0.94	1.02 (0.90-1.17)	0.71	0.96 (0.84-1.11)	0.62
Process of care measures:						
Senior review within 12 hours	0.72 (0.67-0.77)	<0.0001	0.79 (0.72-0.86)	<0.0001	0.76 (0.69-0.83)	<0.0001
CXR within 4 hours	0.93 (0.84-1.23)	0.15	1.1 (0.98-1.25)	0.11	1.02 (0.89-1.17)	0.75
Antibiotics within 4 hours	1.01 (0.93-1.09)	0.85	1.13 (1.03-1.24)	0.01	1.14 (1.02-1.26)	0.02
Guideline concordant antibiotics:	1 (0.93-1.07)	0.96	1 (0.92-1.09)	0.94	1.03 (0.94-1.13)	0.5

Table 6.3: Adjusted odds ratios with 95% confidence intervals and p values for outcomes and process of care measures between weekday and weekend admission groups subdivided by CURB65 severity category. LOS = length of stay. The baseline group for comparison is the weekday admission group. Outcomes are adjusted for: Age category, cardiac failure, other chronic heart disease (excluding hypertension), cerebrovascular disease, liver disease, chronic kideney disease, maligancy, copd, other chronic lung disease, diabetes, dementia.

6.4 Discussion

Our main finding is that 30-day in-patient mortality, adjusted for disease severity and co-morbidities, was slightly lower for adults admitted to hospital with CAP at weekends compared to weekdays. In addition, patients admitted at weekends were more likely to receive antibiotics within four hours.

The finding of lower mortality is in contrast to published evidence on the 'weekend effect', much of which is not disease specific. Evidence related specifically to pneumonia is mixed. In Japan, *Uematsu et al.* found a 10% higher adjusted total inpatient mortality for weekend admissions with severe pneumonia (165). In Australia, *Baldwin et al.* found no association between day of week admitted and mortality in patients with pneumonia (166). In England, analysis of administrative inpatient data linked to mortality data from 2004-12 found marginally increased mortality for patients with pneumonia presenting at the weekend (aOR 1.037, 95% CI 1.035-1.049) (167). The association observed by this group was stronger in time sensitive conditions, such as stroke or pulmonary embolus (167). International differences in healthcare systems may contribute to the mixed findings in these studies.

The slightly lower adjusted mortality in the weekend group may reflect more rapid access to time-critical aspects of care, as evidenced by increased access to antibiotics within four hours of admission. A shorter time to first antibiotics has been associated with lower mortality in adults hospitalised with CAP.(168) We found that weekend admissions were twice as likely to be admitted via ED; this has been associated with shorter time to CXR and first antibiotics (162). In a previous UK study, *Meacock et al* demonstrated that the observed weekend effect was largely attributable to 'direct' admissions from the community rather than through ED (169).

Whether these associations account for some of the observed differences in mortality between groups is not determined.

We observed an apparent mismatch in LOS findings in the weekend group, namely a higher proportion with a below or equal to median LOS yet a lower proportion with LOS ≤1 day. This finding likely reflects the real-world difficulties of discharging patients at the weekends due to decreased staffing and differences in the interface between tertiary hospitals and community care. This finding was robust when tested using a competing risk analysis and consistent with previously published evidence; the average LOS is shorter for the weekend group, by one day or less in most studies (170).

6.4.1 Strengths and limitations:

The use of a large national database of clinician and radiology confirmed pneumonia including data on co-morbidity and severity is a strength of this analysis. Unlike administrative datasets that rely on coded data with inherent inaccuracies, our dataset is comprised of clinician and radiology confirmed CAP, reducing misclassification bias from inclusion of patients without CAP (171). Data on co-morbidity and severity of CAP on admission allowed appropriate case-mix adjustment. A previous meta-analysis examining the weekend effect found that studies including measures of acute physiology in their statistical adjustment reported estimates of increased mortality that were 15% lower than studies without adjustment for these measures, highlighting the importance of robust case-mix adjustment (170). The availability of process of care measures allowed us to examine possible explanations for observed differences.

Limitations of the study include: i) the seasonality of the data (winter only), ii) limited microbiological and vaccination data and iii) the proportion of cases missing data on adjustment variables. The winter months represent

a time when respiratory infections are at their commonest and physician awareness regarding best practice in management of pneumonia may be heightened, driving improved care. However, it is also a time where health services are under the greatest pressure; this may produce the opposite effect. It is difficult to predict the combined effect of these potential biases. The BTS dataset lacks robust data on microbiology and vaccination. A higher proportion of antibiotic-resistant, or more virulent, pathogens within the sicker weekend group, compared to the weekday group, cannot be excluded. If present, the direction of bias would be towards a higher weekend mortality and would mean the study findings are conservative. In the UK, priority groups for influenza and pneumococcal vaccination are identified according to older age and presence of co-morbid illnesses. Overall, there were no major baseline differences between the two groups that would suggest a large difference in relation to eligibility for vaccination although we cannot exclude the possibility that vaccine uptake may have been higher in one of the groups.

The relatively high proportion of missing data for some adjustment variables reflects the fact that the primary dataset is derived from national audit data that relies on data entry by participating institutions. As cases are reviewed retrospectively for inclusion in the audit, we have no reason to believe that the groups would differ significantly in the proportions with missing data. Finally, common to observational cohort studies, causal inferences cannot be made in the associations identified.

6.4.2 Conclusions:

There was no evidence of increased mortality for patients admitted at the weekend with CAP despite an older cohort with higher severity disease. The slightly lower adjusted mortality in the weekend group may reflect more rapid access to time-critical aspects of care, as evidenced by increased access to antibiotics within four hours of admission.

Our findings support the continued use of established guidelines for use by non-specialist clinical staff outside normal clinical hours with a focus on timely receipt of antibiotics.

Chapter 7 Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against vaccine serotype pneumococcal pneumonia in adults: A case-control test-negative design study

7.1 Introduction

Streptococcus pneumoniae is widely accepted as the most common bacterial cause of community-acquired pneumonia (CAP) worldwide and is associated with substantial morbidity, mortality and economic burden (15, 172). Two different types of pneumococcal vaccine are currently available: the 23-valent pneumococcal polysaccharide vaccine (PPV23) and pneumococcal conjugate vaccines (PCVs). In the UK, a national pneumococcal vaccination policy with 7-valent PCV was introduced for children under 2 years old in September 2006 and replaced with the 13-valent PCV in 2010 (66). Subsequent reductions in invasive pneumococcal disease (IPD) and nasopharyngeal carriage due to vaccine serotypes in children were observed (173). Reductions in vaccine type IPD and non-invasive pneumococcal pneumonia (NIPP) in adults followed, largely due to herd protection effects (173). However, with the emergence of replacement serotypes in the UK, recent studies have observed increases in the incidence rates of IPD and pneumococcal pneumonia due to non-PCV13 serotypes (174, 175).

Vaccination with PPV23, containing the PCV13 serotypes (except 6A) and 11 additional serotypes (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F) has been available in England to those ≥65 years and those in a clinical risk group since 2003, with coverage in those ≥65 years at 69.5% in

March 2018 (70). PPV23 vaccination has been found to be effective in preventing IPD and displays a waning effect with time from vaccination (147, 176). However, the effectiveness of PPV23 against pneumococcal pneumonia is controversial (177). There are scant data regarding PPV23 serotype-specific vaccine effectiveness (VE) against NIPP in the setting of a well-established national infant pneumococcal vaccination programme. Such data are important to inform future adult vaccination policies (178).

The aim of this work was to evaluate the VE of PPV23 against vaccine-type pneumococcal pneumonia in adults hospitalised with CAP. Secondary aims were to (i) estimate VE in defined patient subgroups, (ii) estimate VE against pneumococcal serotypes not covered by herd protection from PCV13 (PPV23/non-PCV13 pneumonia), and (iii) examine the effect of time since vaccination on VE.

7.2 Methods

7.2.1 Study design

This study is a secondary analysis of data collected from a prospective observational cohort study of consecutive adult patients with CAP admitted to 2 large university hospitals in Nottingham, UK, between September 2013 and August 2018. The primary study was designed to determine trends in pneumococcal serotypes in adults hospitalised with CAP over time; study details including epidemiological results arising over the first 10 years of study have been published previously (175, 179). Ethical approval for the primary study was provided by the Nottingham Research Ethics Committee (REC reference 08/H0403/80). For this analysis, as with previous influenza and pneumococcal vaccine studies estimating VE in a real-world population, a nested case-control test-negative design was used (180, 181). The exposure of interest was PPV23 vaccination prior to the index admission, and the primary outcome was PPV23 vaccine serotype pneumococcal pneumonia.

7.2.2 Study cohort

Study eligibility criteria, recruitment and microbiological processes have been described in full previously (175). Briefly, patients aged ≥16 years presenting with one or more acute lower respiratory tract symptom, evidence of acute infiltrates consistent with respiratory infection on admission chest radiograph and treated for a diagnosis of CAP were eligible. Exclusion criteria included prior hospitalisation within 10 days of index admission, a diagnosis of tuberculosis or post-obstructive pneumonia. Following informed consent, information on demographics and clinical characteristics (including potential confounders) were collected using a standardised proforma via researcher interview and medical records. For this analysis, only patients providing a sample subjected to pneumococcal serotype-specific testing were included. Pneumococcal serotype was identified using the following: (i) for bacteraemic cases: slide agglutination tests with latex antisera (ImmuLex Pneumotest kit) or standard factor sera (SSI Diagnostica, Hillerød, Denmark), or (from October 2017) whole genome sequencing; (ii) for NIPP cases: multiplex immunoassay (Bio-plex24) applied to urine samples to detect 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 plus some cross-reactive serotypes (175, 182, 183).

7.2.3 Case groups

The primary case group of interest was patients with pneumococcal pneumonia caused by PPV23 vaccine serotypes. The secondary case group comprised patients with PPV23/non-PCV13 serotype pneumonia (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F); cases caused by PPV23/PCV13 serotypes were censored from analysis of the secondary group.

7.2.4 Control group

A patient with non-PPV23 vaccine serotype pneumococcal disease or nonpneumococcal pneumonia was defined as a control. This included Bio-plex24 negative cases (pneumonia of alternate aetiology), Bio-plex24 assay common polysaccharide (CPS)-antigen–only positive cases, and non-PPV23 vaccine-type *S. pneumoniae* cases. No matching of cases with controls was conducted. The control group remained the same for both primary and secondary analyses and was restricted as appropriate for subgroup analyses.

7.2.5 Multiple serotypes identified

Where multiple serotypes were identified in a single patient, these were excluded from the primary analysis if the identified serotypes crossed the case-control definition. For analysis of the PPV23/non-PCV13 group, a case was included if one of the identified serotypes fulfilled the case definition and none of the identified serotypes fulfilled the definition of a control.

7.2.6 Vaccine status

At the time of hospital admission, patient self-reported pneumococcal vaccine status was recorded. Date of vaccination was confirmed from primary care records where available. In the primary analysis, patients were considered vaccinated if (i) vaccine status was confirmed via primary care records or (ii) they self-reported having had the vaccine. Details on influenza vaccination (a potential confounding variable) were also collected. A patient was considered vaccinated against influenza if they had received the influenza vaccine in the 12 months prior to index admission only (confirmed and self-reported). Sensitivity analysis of the primary outcome including only patients with vaccine status confirmed via primary care records was performed. Cases with vaccination less than 14 days prior to disease were excluded.

7.2.7 Statistical analysis

The case and control groups and vaccinated and unvaccinated individuals were compared using the appropriate summary statistic for the variable (proportions for binary variables, median and interquartile range [IQR] for non-normally distributed continuous variables). Odds ratios with 95% CIs and *p*-values for significance testing were calculated for binary variables. Logistic regression and chi-squared tests for trend were used to test associations between ordered categorical exposure variables (severity category, baseline performance status as defined by the ECOG Performance Scale) (184) and binary outcomes. Patients with missing data on vaccine status were excluded from the primary analysis. To investigate reporting bias, sensitivity analysis was performed by including this group as either vaccinated or unvaccinated in turn.

Adjusted odds ratios were derived using multivariable logistic regression models to describe the odds of case status between vaccinated and unvaccinated individuals; the outcome variable was case versus control. For the main analysis following modelling using Directed Acyclic Graphs (www.dagitty.net) (164), confounders included in the model a priori were age, sex, flu vaccination status in the past year, and clinical at-risk groups defined in accordance with Public Health England's 'Immunisation against Infectious Diseases' (The Green Book) (66). Influenza vaccination was included as an a priori confounder due to evidence that it is associated with PPV23 uptake and linked with health-seeking behaviours (185). Smoking status was tested as an adjustment variable; it did not alter the results and so was not included. To account for change in serotype distribution over study years, year of index admission was tested as an adjustment variable; it did not alter the results and was not included in the final model. Likelihood ratio testing of continuous variables was performed to determine best fit (continuous versus grouped). VE estimates were calculated as (1 − odds ratio) × 100%. Subgroup analyses were performed with the whole

cohort (cases and controls) restricted to those who were: (i) vaccine eligible under current UK pneumococcal vaccine policy, (ii) those ≥65 years old, and (iii) those ≥75 years old.

A secondary analysis examining the effect of time since vaccination on VE including patients with confirmed vaccine status only was performed using a categorical variable with 5 levels for time interval between vaccination date and index admission (never vaccinated, vaccinated 0–5 years, 5–10 years, 10–15 years, and ≥15 years prior to admission). A logistic regression model was used to derive the odds of being a case in each vaccination category compared to those never vaccinated. A *p*-trend across the groups was calculated using the likelihood ratio test. To further investigate long-term decline in VE, a categorical variable for each individual year from vaccination to index admission (up to 24 years) and a cubic spline model were calculated with knots at 1, 4, and 8 years (176). All analyses were performed using Stata 16 (186). The study was conceived in 2017, and a prospective analysis plan was written by HL, TM, and WSL in March 2019. Following peer review, a serotype-specific VE analysis and an analysis of all PPV23 cases excluding serotype 5 were performed.

7.3 Results

7.3.1 Cohort description

During the 5-year study period, of 2,447 eligible study participants, 54 were excluded as no vaccine status was available, leaving 2,393 patients. In this cohort of predominantly NIPP, pneumococcal serotype was detected by Bio-plex24 assay in 968 (40.5%) and by blood culture in 110 (4.6%) patients, respectively. In 36 patients, multiple serotypes crossing the case-control definition were detected, leaving 2,357 patients for the primary

analysis. The most common serotypes detected were serotype 3 (*n* = 197), 8 (*n* = 192), 12F (*n* = 60), 15A (*n* = 54), and 5 (*n* = 41).

7.3.2 Comparison of the vaccinated versus unvaccinated groups

Of 2,357 patients, vaccine status was obtained from primary care records in 1,820 (77.2%) patients and was self-reported in 537 (32.8%). Mean time between vaccination and index admission was 10.3 (SD 5.8) and 10.4 (SD 5.2) years in the cases and controls, respectively. The shortest interval between vaccination and index admission was 47 days. Vaccinated patients were older (74.1 versus 57.4 years, $p < 0.001$) with a poorer baseline performance status (p-trend < 0.0001) and higher severity disease on admission (29.7% versus 15.5% high severity by CURB65 category; p-trend < 0.001) (Table 7.1). They were more likely to have comorbid diseases except liver disease, alcohol dependence, and asthma. Prior vaccination with PCV13 in our cohort was very low at <0.5%.

Table 7.1 - Characteristics of the Unvaccinated and Vaccinated patient cohorts

	Unvaccinated patients	**Vaccinated patients**	**Odds Ratio**	**95% Confidence Interval**	**p-value**
Number	1119	1238			
Mean Age (SD)	57.4 (19.0)	74.1 (13.5)	1.05	1.05-1.06	**<0.0001**
Sex (male %)	619 (55.3)	654 (52.8)	1.01	0.93-1.29	0.26
Residential care	30 (2.7)	51 (4.1)	1.56	0.98-2.47	0.06
Baseline PS (%):					
0	480 (42.9)	327 (26.4)	1		
1	351 (31.4)	465 (37.6)	1.94	1.60-2.37	
2	155 (13.9)	259 (20.9)	2.45	1.92-3.13	
3	49 (4.4)	63 (5.1)	1.89	1.27-2.81	
4	36 (3.2)	35 (2.8)	1.43	0.88-2.32	**<0.0001***
Missing	48 (4.3)	89 (7.2)			
Severity (%):					
Low	695 (62.1)	438 (35.4)	1		
Moderate	251 (22.4)	432 (34.9)	2.73	2.24-3.32	
Severe	173 (15.5)	368 (29.7)	3.38	2.72-4.19	**<0.0001***
Co-morbidities:					
Malignancy	80 (7.2)	140 (11.3)	1.65	1.24-2.20	0.0006
Liver Disease	31 (2.8)	19 (1.5)	0.55	0.31-0.97	0.04
CCF	45 (4.0)	100 (8.1)	2.1	1.46-3.01	<0.0001
CVA	45 (4.0)	134 (10.8)	2.9	2.04-4.11	<0.0001
Renal disease	68 (6.1)	156 (12.6)	2.22	1.65-3.01	<0.0001
Diabetes	122 (10.9)	254 (20.5)	2.11	1.67-2.67	<0.0001
IHD	73 (6.5)	178 (14.4)	2.41	1.80-3.21	<0.0001
Cognitive impairment	23 (2.1)	58 (4.7)	2.34	1.43-3.83	0.0005
Asthma	130 (11.6)	117 (9.5)	0.79	0.61-1.03	0.09
COPD	158 (14.1)	404 (32.6)	2.95	2.39-3.64	<0.0001
Chronic heart disease	110 (9.8)	253 (20.4)	2.36	1.85-3.00	<0.0001

Chronic lung disease	184 (16.4)	454 (36.7)	2.94	2.41-3.60	<0.0001
Hypertension	193 (17.3)	378 (30.5)	2.11	1.73-2.57	<0.0001
Alcohol	42 (3.8)	18 (1.5)	0.38	0.22-0.66	0.0004
Immunosuppression	42 (3.7)	66 (5.3)	1.44	0.97-2.15	0.07

Table 7.1 - Characteristics of the unvaccinated and vaccinated patient cohorts. Unadjusted odds ratios with 95% CIs are presented with *p*-values. The baseline group for all analysis is the unvaccinated cohort. **p*-Trend derived from chi-squared test for trend.

7.3.3 Comparison between cases of PPV23 serotype pneumonia and controls

There were 717 cases of PPV23 serotype pneumonia (48% vaccinated) and 1,640 controls (54.5% vaccinated). Compared to controls, cases were of a similar age (66.5 versus 65.4 years, $p = 0.18$) but were less likely to be male (47.6% versus 56.9%, $p < 0.0001$) (Table 7.2). Cases had a better baseline performance status (p-trend = 0.01), had higher severity disease on admission (26.2% versus 21.5% high severity by CURB65; p-trend = 0.01), were less likely to have malignancy or cardiac disease, but were more likely to be alcohol dependent.

Table 7.2 - Characteristics of cases and control groups for the primary analysis.

	Controls *N* (%)	**Case PPV23 Disease *N* (%)**	**Odds Ratio (95% CI)**	***p*-Value**
Number	1,640	717		
Mean Age (SD)	66.5 (18.3)	65.4 (18.7)	1.00 (0.99–1.00)	0.18
Sex, Male	932 (56.9)	341 (47.6)	0.69 (0.58–0.82)	**<0.001**
Residential Care	57 (3.5)	24 (3.4)	0.96 (0.59–1.56)	0.88
Baseline Performance Status				
0	522 (31.8)	285 (39.8)	1	
1	587 (35.8)	229 (31.9)	0.71 (0.58–0.88)	
2	291 (17.7)	123 (17.1)	0.77 (0.60–1.00)	
3	81 (4.9)	31 (4.3)	0.70 (0.45–1.09)	
4	55 (3.4)	16 (2.2)	0.53 (0.30–0.95)	**0.009***
Missing	104 (6.3)	33 (4.6)		
Severity by CURB65 Score				
Low	820 (50.0)	313 (43.7)	1	
Moderate	467 (28.5)	216 (30.1)	1.21 (0.98–1.49)	
Severe	353 (21.5)	188 (26.2)	1.40 (1.12–1.74)	**0.009***
Comorbidity				
Malignancy	168 (10.3)	52 (7.3)	0.68 (0.49–0.95)	**0.02**
Liver disease	31 (1.9)	19 (2.7)	1.41 (0.79–2.52)	0.24
Cardiac failure	112 (6.8)	33 (4.6)	0.66 (0.44–0.98)	**0.04**
Cerebrovascular disease	127 (7.7)	52 (7.3)	0.93 (0.67–1.30)	0.68
Renal disease	157 (9.6)	67 (9.3)	0.97 (0.72–1.32)	0.86
Diabetes	266 (16.2)	110 (15.3)	0.94 (0.73–1.19)	0.59
IHD	188 (11.5)	63 (8.8)	0.74 (0.55–1.00)	**0.05**

Cognitive impairment	55 (3.4)	26 (3.6)	1.08 (0.67–1.74)	0.74
Asthma	163 (9.9)	84 (11.7)	1.20 (0.91–1.59)	0.19
COPD	393 (24.0)	169 (23.6)	0.98 (0.80–1.20)	0.84
Chronic heart disease	277 (16.9)	86 (12.0)	0.67 (0.52–0.87)	**0.003**
Chronic lung disease	446 (27.2)	192 (26.8)	0.98 (0.80–1.19)	0.83
Hypertension	389 (23.7)	182 (25.4)	1.09 (0.89–1.34)	0.39
Alcohol	34 (2.1)	26 (3.6)	1.78 (1.06–2.99)	**0.03**
Immunosuppression	75 (4.6)	33 (4.6)	1.01 (0.66–1.53)	0.98

*Patient characteristics in the control and case groups. Unadjusted odds ratios with 95% CIs and p-values are presented (p-values in bold <0.05). The baseline group for comparison is the control group in all analysis. *p-Trend derived from chi-squared test for trend.*

7.3.4 Primary analysis: VE against PPV23 serotypes

In the primary analysis of all cases of PPV23 serotype disease, the crude VE estimate was 23% (95% CI 8%–35%) (Table 7.3). Following adjustment for age, sex, flu vaccination status, and clinical risk factors, estimated VE was 24% (95% CI 5%–40%, $p = 0.02$). Full model parameters are available in Table 7.4. Adjusted estimates of VE (aVE) were similar in patient subgroups restricted by (i) vaccine eligibility (n = 1,768, aVE 23%, 95% CI 1%–40%, $p = 0.04$) and (ii) age ≥ 65 years (n = 1,407, aVE 20%, 95% CI −5% to 40%, $p = 0.11$). In patients aged ≥75 years (n = 905), aVE was only 5% (95% CI −37% to 35%, $p = 0.77$). The mean times from vaccination to index admission with CAP for these patient subgroups were 10.4 (SD 5.4) years, 10.8 (SD 5.3) years, and 11.8 (SD 4.8) years, correspondingly.

Table 7.3 - Unadjusted VE and aVE estimates

	Cases *N* (%)	Controls *N* (%)	Unadjusted VE % (95% CI)	aVE % (95% CI)	*p*-Value Adjusted Analysis
Primary Analysis: All PPV23 Serotypes					
Whole Cohort					
Number	717	1,640			
Not vaccinated	373 (52.0)	746 (45.5)			
Vaccinated	344 (48.0)	894 (54.5)	**23 (8 to 35)**	**24 (5 to 40)[a]**	**0.02**
Subgroup: Vaccine Eligible					
Number	503	1,265			
Not vaccinated	189 (37.6)	416 (32.9)			
Vaccinated	314 (62.4)	849 (67.1)	19 (−1 to 34)	**23 (1 to 40)[b]**	**0.04**
Subgroup: ≥65 Years					
Number	414	993			
Not vaccinated	133 (32.1)	267 (26.9)			
Vaccinated	281 (67.9)	726 (73.1)	**22 (0 to 39)**	20 (−5 to 40)[c]	0.11
Subgroup: ≥75 Years					
Number	246	659			
Not vaccinated	65 (26.4)	168 (25.5)			
Vaccinated	181 (73.6)	491 (74.5)	5 (−33 to 32)	5 (−37 to 35)[d]	0.77
Secondary Analysis					
PPV23/non-PCV13 Serotypes (Whole Cohort)					

Number	417	1,640			
Not vaccinated	235 (56.4)	746 (45.5)			
Vaccinated	182 (43.7)	894 (54.5)	**35 (20 to 48)**	**29 (6 to 46)[a]**	**0.02**

[a]Adjusted for age, sex, receipt of seasonal flu vaccination, and presence or absence of the following risk factors: malignancy, cardiac failure, cerebrovascular disease, chronic renal disease, chronic liver disease, diabetes, ischaemic heart disease, COPD, other chronic cardiac disease, other chronic lung disease, hypertension, alcohol dependence, and immunosuppression.
[b]Adjusted for age, sex, receipt of seasonal flu vaccination.
[c]Adjusted for age group over 65, sex, receipt of seasonal flu vaccination, and presence or absence of a clinical risk factor.
[d]Adjusted for sex, receipt of seasonal flu vaccination, and presence or absence of a clinical risk factor only.
Unadjusted and adjusted results of the primary analysis, subgroup analysis, and the secondary case group analysis in cases against controls. The baseline group for all analysis is the respective control group. Vaccine exposure confirmed and self-reported yes at any point prior to their index admission. P-values in bold are <0.05.

Table 7.4 - Estimated model parameters for the primary analysis

	OR	95% CI	P value
Previous PPV23 vaccination with PPV23	0.76	0.6-0.95	0.02
Age	1	0.99-1.01	0.51
Sex (male)	0.68	0.57-0.82	<0.0001
Seasonal influenza vaccination	1.01	0.81-1.25	0.96
Risk factors:			
Cancer	0.7	0.5-0.99	0.04
Cardiac failure	1.2	0.58-2.48	0.63
Cerebrovascular disease	1.05	0.74-1.5	0.77
Renal disease	1.05	0.76-1.44	0.78
Liver disease	1.17	0.62-2.21	0.62
Diabetes	0.95	0.73-1.22	0.67
Ischaemic heart disease	1.55	0.71-3.4	0.27
Cognitive impairment	1.12	0.69-1.82	0.66
Chronic obstructive pulmonary disease	1.05	0.62-1.78	0.86
Chronic lung disease	1.01	0.61-1.68	0.97
Hypertension	1.15	0.92-1.43	0.21
Alcohol excess	1.84	1.06-3.21	0.03
Immunosuppression	1.13	0.73-1.75	0.59

Table 7.4. Estimated model parameters for the primary analysis model. Odds ratios, 95% CIs, and *p*-values are displayed.

7.3.5 Secondary analysis: PPV23/non-PCV13 cases and serotype specific

In the secondary analysis of PPV23/non-PCV13 serotype disease (*n* = 417, 43.7% vaccinated), the aVE was 29% (95% CI 6%–46%, *p* = 0.02) (Table 7.3). Similar estimates were observed in the vaccine-eligible (aVE 26%, 95% CI 0%–46%, *p* = 0.05) and ≥65-year-old (aVE 24%, 95% CI −7% to 47%, *p* = 0.12) subgroups. No vaccine effect was observed in the ≥75-year-old subgroup (aVE −2%, 95% CI −65% to 37%, *p* = 0.93). Serotype-specific aVE estimates varied by serotype (Table 7.5). The highest estimates were seen in serotypes 3 (aVE 40%, 95% CI 14%–59%, *p* = 0.01), 12F (aVE 39%, 95% CI −20% to 69%, *p* = 0.15), 19F (aVE 38%, 95% CI −60% to 76%, *p* = 0.32), and 8 (aVE 34%, 95% CI 1%–55%, *p* = 0.04). No vaccine effect was seen for serotypes 19A and 9N, while a negative aVE was observed for serotypes 5 (aVE −144%, 95% CI −503% to 1%, *p* = 0.05) and 11A (aVE −110%, 95% CI −415% to 14%, *p* = 0.1).

Table 7.5 - Serotype Specific Analysis

	Cases N (%)	**Controls N (%)**	**Unadjusted Vaccine Effectiveness % (95% CI)**	**Adjusted Vaccine Effectiveness % (95% CI)**	**p-value adjusted analysis**
Serotype Specific Analysis					
Serotype 3					
Number	197	1640			
Not vaccinated	96 (48.7)	746 (45.5)			
Vaccinated	101 (51.3)	894 (54.5)	12 (-18 to 35)	**40 (14 to 59)**	**0.01**
Serotype 8					
Number	192	1640			
Not vaccinated	119 (62.0)	746 (45.5)			
Vaccinated	73 (38.0)	894 (54.5)	**49 (30 to 62)**	**34 (1 to 55)**	**0.04**
Serotype 12F					
Number	60	1640			
Not vaccinated	39 (65.0)	746 (45.5)			
Vaccinated	21 (35.0)	894 (54.5)	**55 (23 to 74)**	**39 (-20 to 69)**	**0.2**
Serotype 5					
Number	41	1640			
Not vaccinated	9 (22.0)	746 (45.5)			

Vaccinated	32 (78.0)	894 (54.5)	**-197 (-527 to -40)**	-144 (-503 to 1)	0.05
Serotype 11A					
Number	36	1640			
Not vaccinated	11 (30.6)	746 (45.5)			
Vaccinated	25 (69.4)	894 (54.5)	-90 (-288 to 7)	-110 (-415 to 14)	0.1
Serotype 19A					
Number	34	1640			
Not vaccinated	17 (50.0)	746 (45.5)			
Vaccinated	17 (50.0)	894 (54.5)	17 (-65 to 58)	14 (-105 to 64)	0.74
Serotype 9N					
Number	32	1640			
Not vaccinated	13 (40.6)	746 (45.5)			
Vaccinated	19 (59.4)	894 (54.5)	-22 (-150 to 40)	-15 (-173 to 52)	0.75
Serotype 19F					
Number	25	1640			
Not vaccinated	10 (40.0)	746 (45.5)			
Vaccinated	15 (60.0)	894 (54.5)	-25 (-180 to 44)	38 (-60 to 76)	0.32

Table 7.5. Unadjusted and adjusted results of the serotype-specific analysis. *The baseline group for all analysis is the respective control group. Vaccine exposure confirmed and self-reported yes at any point prior to their index admission. Results are adjusted for age, sex, receipt of seasonal flu vaccination, and presence or absence of a clinical risk factor only.*

7.3.6 Sensitivity analysis: Vaccine-confirmed cases

Patients with vaccine status confirmed through primary health records were older (67.9 versus 62.3 years) and more likely to have comorbid disease with higher severity disease on admission (24.2% versus 18.8% high severity disease) (Table 7.6). A higher proportion were vaccinated with PPV23 (59.6% versus 28.7%). Sensitivity analysis of those with confirmed vaccine status produced slightly lower aVE estimates for all PPV23 cases (aVE 19%, 95% CI −5% to 37%, $p = 0.12$) and PPV23/non-PCV13 cases (aVE 21%, 95% CI −10% to 43%, $p = 0.16$) with confidence intervals crossing zero in both instances. There was no change in the primary outcome following sensitivity analysis of those missing both confirmed and self-reported vaccine status ($n = 54$).

Table 7.6 - Characteristics of vaccine confirmed vs self-reported only patients

	Vaccine status confirmed through medical records N (%)	**Self-reported vaccine status only N (%)**	**p-value**
Number	1820	537	
Mean Age (SD)	67.9 (17.8)	62.3 (19.3)	**<0.0001**
Gender (male)	971 (53.3)	303 (56.4)	0.21
Residential care	70 (3.8)	11 (2.1)	0.06
Vaccinated	1084 (59.6)	154 (28.7)	**<0.0001**
Baseline Performance Status:			
0	605 (33.2)	202 (37.6)	
1	618 (34.0)	198 (36.9)	
2	341 (18.7)	73 (13.6)	
3	89 (4.9)	23 (4.3)	
4	56 (3.1)	15 (2.8)	0.05*
Missing	111 (6.1)	26 (4.8)	
Severity by CURB 65 Score:			
Low	821 (45.1)	312 (58.1)	
Moderate	559 (30.7)	124 (23.1)	
Severe	440 (24.2)	101 (18.8)	**<0.0001***
Co-Morbidity:			
Malignancy	171 (9.4)	49 (9.1)	0.54
Liver Disease	36 (2.0)	14 (2.6)	0.37
CCF	128 (7.0)	17 (3.2)	**0.001**
CVA	159 (8.7)	20 (3.7)	**<0.0001**
Renal disease	185 (10.2)	39 (7.3)	**0.04**
Diabetes	307 (16.9)	69 (12.9)	**0.02**
IHD	210 (11.5)	41 (7.6)	**0.01**
Cognitive impairment	72 (4.0)	9 (1.7)	**0.01**
Asthma	187 (10.3)	60 (11.2)	0.55
COPD	467 (25.7)	95 (17.7)	**<0.0001**
Chronic heart disease	309 (17.0)	54 (10.6)	**<0.0001**
Chronic lung disease	526 (28.9)	112 (20.9)	**<0.0001**
Hypertension	457 (25.1)	114 (21.2)	0.06
Alcohol	40 (2.2)	20 (3.7)	0.05
Immunosuppression	80 (4.4)	28 (5.2)	0.42

*Table 7.6 Characteristics of patients in whom the vaccine status was confirmed via primary care compared to those with self-reports only. *p-Trend derived from chi-squared test for trend.*

7.3.7 Time from vaccination

Data on date of vaccination were available for 535 (74.6%) cases of PPV23 serotype disease and 1,285 (78.3%) controls. The *p*-trend across time groups was 0.39, suggesting no association between time since vaccination and being a case (Table 7.7). For PPV23/non-PCV13 serotype disease, an association was observed (*p*-trend = 0.04); the highest aVE seen in those vaccinated within 5 years (aVE 46%) declining to 5% in those vaccinated ≥15 years prior (Table 3).

Table 7.7 - Time from vaccination analysis.

	Number	Adjusted Odds Ratio	*p*-Trend	% aVE (95% CI)
PPV23 Serotypes				
Never	736	1		0
>15 years	228	0.9 (0.62 to 1.3)		10 (−30 to 38)
10–15 years	360	0.71 (0.51 to 0.99)		29 (1 to 49)
5–10 years	293	0.7 (0.49 to 0.98)		30 (2 to 51)
0–5 years	203	1.07 (0.74 to 1.54)	0.39	−7 (−54 to 26)
PPV23/non-PCV13 Serotypes Only				
Never	641	1		0
>15 years	196	0.95 (0.59 to 1.52)		5 (−52 to 41)
10–15 years	324	0.85 (0.56 to 1.29)		15 (−29 to 44)
5–10 years	264	0.81 (0.53 to 1.24)		19 (−24 to 47)
0–5 years	155	0.54 (0.31 to 0.95)	0.04	46 (5 to 69)

Adjusted odds ratios for case status between vaccinated and unvaccinated individuals in each time from vaccination group, compared to the baseline never vaccinated group. The p-trend across groups is presented. All estimates are adjusted for age, sex, receipt of seasonal flu vaccination, and presence or absence of the following risk factors: malignancy, cardiac failure, cerebrovascular disease, chronic renal disease, chronic liver disease, diabetes, ischaemic heart disease, COPD, other chronic cardiac disease, other chronic lung disease, hypertension, alcohol dependence, and immunosuppression. VE estimates are calculated as (1 − aOR) × 100.

A cubic spline model demonstrating change in VE with time since vaccination is shown in Fig 7.1. For PPV23 serotype disease, an inverted-U shape was observed suggesting a negative VE in those most recently vaccinated (Fig 7.1A). A post hoc descriptive analysis of cases vaccinated 0–5 years prior to admission found that the most commonly identified serotype was serotype 5 (*n* = 23, 34.6%) equating to 75.8% (23/33) of all serotype 5 cases. When serotype 5 cases were excluded from the PPV23 serotype case group, the inverted-U shape was not observed (Fig 7.1C).

Figure 7.1 - VE against time since vaccination using the spline model.

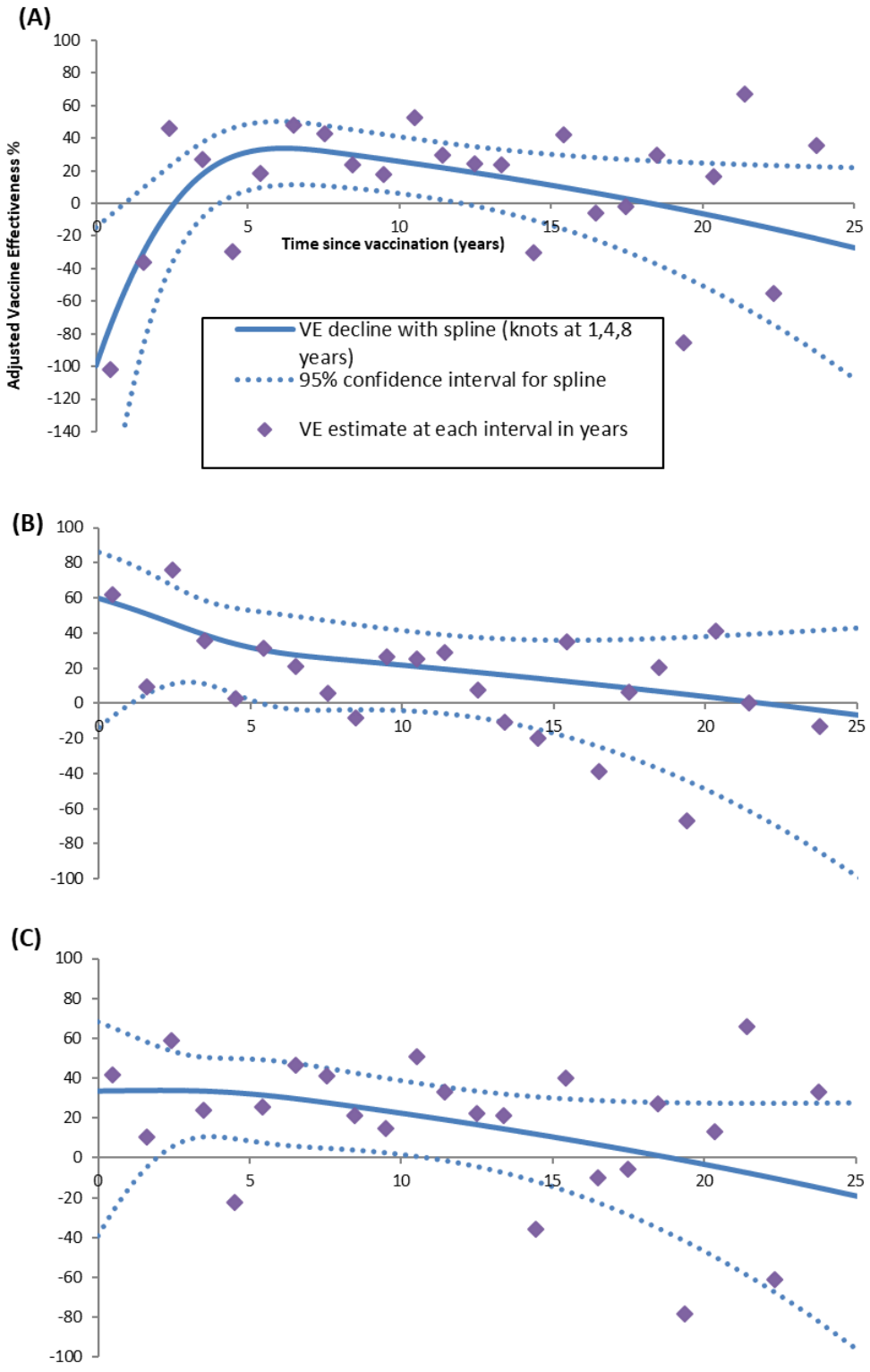


Fig 7.1. VE against time since vaccination using the spline model. *VE by time since vaccination (in years) using the cubic spline model for the following case groups: (A) all PPV23 serotype disease, (B) PPV23/nonPCV13 serotype disease, and (C) all PPV23 serotype disease excluding serotype 5. Individual estimates for each year are shown but are based on small participant numbers within each year.*

Table 7.8 - Sub-analysis of healthy 60-75 year olds

	Cases N (%)	**Controls N (%)**	**Unadjusted Vaccine Effectiveness % (95% CI)**	**Adjusted Vaccine Effectiveness % (95% CI)**	**p-value adjusted analysis**
Primary case group – all PPV23:					
Number	65	109			
Not vaccinated	40 (61.5)	63 (57.8)			
Vaccinated	25 (38.5)	46 (42.2)	14 (-61 to 54)	12 (-67 to 53)	0.7
Secondary case group – PPV23/non-PCV13					
Number	33	109			
Not vaccinated	23 (69.7)	63 (57.8)			
Vaccinated	10 (35.0)	46 (42.2)	40 (-38 to 74)	39 (-43 to 74)	0.26

Table 7.8. Subanalysis of the cohort restricted to 60- to 75-year-olds with no known risk factors. *Unadjusted and adjusted results of the primary analysis and the secondary case group analysis in cases against controls. The baseline group for all analysis is the respective control group. Vaccine exposure confirmed and self-reported yes at any point prior to their index admission. Adjusted for sex only.*

Table 7.9 - Sensitivity analysis excluding Serotype 5 from primary case group (All PPV23)

	Cases N (%)	**Controls N (%)**	**Unadjusted Vaccine Effectiveness % (95% CI)**	**Adjusted Vaccine Effectiveness % (95% CI)**	**p-value adjusted analysis**
Number	676	1640			
Not vaccinated	364 (53.9)	746 (45.5)			
Vaccinated	312 (46.2)	894 (54.5)	**28 (14 to 40)**	**26 (7 to 42)***	**0.01**

Table 7.9. Subanalysis excluding serotype 5 from the primary analysis group (all PPV23 serotypes). *Adjusted for age, sex, receipt of seasonal flu vaccination, and presence or absence of the following risk factors: malignancy, cardiac failure, cerebrovascular disease, chronic renal disease, chronic liver disease, diabetes, ischaemic heart disease, COPD, other chronic cardiac disease, other chronic lung disease, hypertension, alcohol dependence, and immunosuppression. ^Adjusted for age, sex, receipt of seasonal flu vaccination.*

7.4 Discussion

The key study findings are that PPV23 vaccination provides moderate long-term protection in vaccinated individuals against hospitalisation with PPV23 serotype pneumonia (aVE 24%), with similar levels of protection evident for patient subgroups restricted to those who are vaccine eligible according to UK immunisation policy recommendations (aVE 23%) and patients aged ≥65 years (aVE 20%) but not for patients aged ≥75 years (aVE 5%). We also found protection against hospitalisation with PPV23/non-PCV13 serotype pneumonia to be similar (aVE 29%).

To our knowledge, only 2 other studies have previously reported on the serotype-specific effectiveness of PPV23 against pneumococcal pneumonia. Slightly higher VE estimates were reported by Suzuki and colleagues in their study of PPV23 effectiveness in adults over the age of 65 in Japan (181). Using a similar test-negative design, they estimated PPV23 VE to be 33.5% (95% CI 5.6%–53.1%) against PPV23 serotypes and 27.4% (95% CI 3.2%–45.6%) against all pneumococcal pneumonia. There are differences that may account for our lower VE estimate. Firstly, our primary analysis included all vaccinated patients regardless of time of vaccination, whereas Suzuki and colleagues only considered a patient vaccinated if they had received the vaccine within 5 years prior to their index admission. Our estimates therefore represent long-term VE estimates. Secondly, our study took place in the setting of established PCV13 use within a strong national childhood vaccination program and resultant herd protection against these serotypes. In contrast, PCV13 replaced PCV7 in the Japanese childhood vaccination program only in the last 6 months of the study by Suzuki and colleagues.

A matched case-control study by Kim and colleagues of patients ≥65 years of age in the Republic of Korea found similar aVE estimates to ours in those aged 65–75 (aVE 21.0%) but no effect in those ≥75 years (aVE

−35%) (187). Of note, the median interval from vaccination to disease was short at 15 months, representing peak VE, and therefore their estimates are lower than might be expected. Both Suzuki and colleagues and Kim and colleagues relied on culture-based techniques of pneumococcal isolates to identify serotype (181, 187). As only a minority of patients with pneumococcal infection usually have positive respiratory and/or blood cultures, those studies represent a selected patient group (188).

Our VE estimates are lower than those reported for PPV23 vaccination against IPD. In a Cochrane review by Moberley and colleagues, the pooled odds of vaccination in cases of IPD was 0.26 (*n* = 11 randomised controlled trials [RCTs], 95% CI 0.14–0.45) and in vaccine-type IPD was 0.18 (*n* = 5 RCTs, 95% CI 0.1%–0.31%), equating to VE estimates of 74% and 82%, respectively (147). As included clinical trials had shorter follow-up periods (2–3 years) compared to the mean time since vaccination observed in our study (10.4 years), their estimates likely represent maximal VE post-vaccination. In addition, Moberley and colleagues included older studies (pre-1970) that predominantly included cohorts of young, healthy individuals for whom the effect of immunosenescence is less important and consequently where VE estimates may be expected to be higher. Subgroup analysis by Moberley and colleagues of patients with known chronic disease from high-income countries found no protective effect, suggesting differential VE depending on underlying disease within IPD (147). Using more recent UK data, Djennad and colleagues estimated VE of PPV23 against vaccine-type IPD in patients ≥65 years to be only slightly higher than those observed in our study of predominantly NIPP (IPD aVE 27%, 95% CI 17%–35%, bacteraemic pneumonia aVE 29%, 95% CI 17%–40%) (176). Overall, it remains likely that PPV23 VE is greater against IPD than NIPP, but the size of difference may not be as large as previously estimated.

In our cohort of predominantly NIPP, we found the aVE for serotype 3 was 40% (95% CI 14%–59%). This is similar to VE estimates by Suzuki and colleagues (41.2%, 95% CI −10.8% to 68.8%) (181). These results suggest that moderate direct protection is afforded by PPV23 against serotype 3 NIPP. Similar direct effects against serotype 3 NIPP in adults have been observed following PCV13 vaccination (189). In contrast, in relation to adult IPD, Djennad and colleagues found no vaccine effect of PPV23 against serotype 3 (176). Taken together, these results suggest that VE of PPV23 against serotype 3 may vary according to type of pneumococcal disease.

PPV23 induces an immune response via B cells in a time- and dose-dependent manner; due to its T-cell–independent mechanism, it is not expected to provide lifelong immunity via immunological memory (190). The duration of protection afforded by the PPV23 vaccine is estimated at between 3 and 10 years (191, 192). Djennad and colleagues reported a decrease in VE estimates against PPV23 serotype disease ≥5 years since vaccination in their IPD cohort (0–2 years VE 41%; ≥5 years VE 23%) (176). Our time interval analyses suggest a loss of protection in those vaccinated 10 to 15 years previously. This represents a longer durability of protection than might be expected from immunogenicity studies alone. However, our time-dependent estimates lack precision due to sample size limitations and may be affected by survival bias in those furthest from vaccination.

VE of PPV23 is known to differ by serotype within IPD (176). In a post hoc analysis, we observed that serotype 5 was responsible for the largest proportion (34.3%) of cases of PPV23 serotype pneumonia within 0–5 years of vaccination. Since the introduction of PCV vaccines, serotype 5 has become an uncommon cause of IPD though it continues to be associated with cases of NIPP both in the UK and the US (175, 193, 194). Prior to the introduction of PCV vaccines, it was considered a low-carriage,

high-virulence serotype that could occur in disease outbreaks (195, 196). In our study, cases of serotype 5 pneumonia were spread evenly across the 5 years of the study, and we found no evidence for temporal clustering. Pimenta and colleagues recently reported other Streptococcal strains (*S. infantis*, *S. mitis*, and *S. oralis*) expressing serotype 5 capsule (197). These pathogens commonly colonise the nasopharynx and mouth although they are not normally associated with a clinical diagnosis of CAP. The Bio-plex24 assay is highly sensitive (182). It is therefore possible that there is a nonpneumococcal provenance for the detected serotype 5 antigen in our cases. However, such cross-reactivity would not in itself explain the differential effect in vaccinated and unvaccinated patients. We are not aware of any previous data, nor mechanism, to suggest that PPV23 vaccination might increase the risk of serotype 5 pneumonia and are currently unable to explain why 75% of cases of serotype 5 pneumonia occurred within 5 years of PPV23 vaccination in our study cohort. Accepting the possibility of a serotype 5 outbreak disproportionately affecting vaccinated individuals would mean that our estimates of PPV23 VE are conservative. Our observations around serotype 5 warrant further study, including confirmation in a separate cohort of patients.

Our reported VE of 24% indicates a 24% reduction in disease occurrence among the vaccinated group. For comparison, recent published VE in the UK for the seasonal influenza vaccine vary by year between 15.0% in 2017/18 and 55.4% in 2015/16 and further by strain and age group (198). These estimates are derived from cohorts vaccinated within the annual flu season and represent short-term VE estimates. The reported VE of the COVID-19 BioNTech Pfizer BNT162b2 vaccine is 70% at 21 days and 85% 7 days after two doses (199). Across COVID-19 vaccines, VE estimates against infection and symptomatic disease decrease by 20-30 percentage points by 6 months likely due to waning immunity (200). Although higher than our reported VE estimates for the PPV23 vaccine, these represent

short-term VE estimates. The mean time since vaccination observed in our study was 10.4 years, representing long-term VE. Public health policies encouraging PPV23 vaccine uptake in target groups should clearly explain the context of the results in the terms of long-term protection.

7.4.1 Strengths and limitations

The main strengths of this study are (i) the use of a serotype-specific multiplex urine assay allowing analysis of VE in both IPD and NIPP across all serotypes included within the PPV23 vaccine, (ii) analysis based on a large cohort of consecutively consented patients without knowledge of the causative serotype at the time of recruitment, thereby minimising selection bias, and (iii) findings set in the background of a strong national PCV13 childhood vaccination programme providing well-established adult herd protection effects. Vaccine status, including date of vaccine, was confirmed through primary care records in a high proportion of patients, thus minimising the effect of recall and misclassification bias. The accuracy of those with self-reported and confirmed vaccine status was 82.7% for those who self-reported as ‘vaccinated’ and 56.1% for those who self-reported as ‘not vaccinated’; the direction of bias when including self-reported vaccine status is therefore towards a more conservative VE estimate (201).

The study is subject to the inherent biases common to case-control studies; however, the main limitation is lack of power. Due to relatively high vaccination rates in both case and control groups, our analysis is underpowered to reject the null hypothesis (that there is no vaccine effect observed); 2,100 patients would be required in each outcome group for 80% power at a significance level of 0.05 for a VE of 22%, estimated on the vaccine exposure within the whole cohort. The statistically significant results observed therefore are likely to represent true findings. However, the study sample was not large enough to enable robust subgroup analyses of VE by age groups above 65 years. Secondly, of those

identified as eligible for the cohort study on which this analysis was conducted, patients in whom study consent was not obtained were older (median age 82.2 years) with more comorbid disease (175). Therefore, VE estimates presented here may be less applicable to persons aged above 80 years (202). Due to the retrospective nature of the study, adjusting by time since vaccination is not possible in the unvaccinated cohort. Our case group were more likely to be female. Close contact with children has previously been found to be associated with an increased risk of pneumococcal disease (203, 204). The observed female predominance in cases may reflect sex differences in level of close contact with children.

7.4.2 Conclusions

In the setting of an established national childhood PCV13 vaccination programme, PPV23 vaccination in clinical at-risk patient groups and adults ≥65 years of age appears moderately effective against hospitalisation with PPV23 serotype pneumococcal pneumonia.

Chapter 8 Discussion

This chapter collates the key findings from this thesis, discusses clinical implications and ideas for further research. It is subdivided by topic into PPV23 vaccination, healthcare outcomes and variation.

8.1 Healthcare Outcomes

8.1.1 Key Findings

This thesis examines the several determinants of adverse healthcare outcomes in adults hospitalised with CAP. Greater social deprivation was associated with increased 30-day mortality in persons aged <65 years, but not in older adults. Regardless of age, increasing deprivation was associated with increasing risk of hospital readmission. The most common reason for readmission within 30-days of index CAP admission was pneumonia. Inpatient mortality was high in this group; they were over twice as likely to die during readmission than those readmitted for other reasons. There was no evidence of increased mortality for patients admitted at the weekend with CAP despite an older cohort with higher severity disease.

8.1.2 Clinical Implications

This work has several implications for the management of patients hospitalised with CAP. The COVID-19 pandemic has highlighted established health inequalities and led to a recognised need for public health strategies to combat adverse outcomes in deprived areas (154). Our analysis demonstrates adverse outcomes associated with deprivation are also present in all-cause CAP. Strategies to decrease health inequalities associated with deprivation should focus on reducing both index-admission mortality and subsequent readmission related to all acute severe respiratory infections, including COVID-19. In addition, our findings support the continued use of established guidelines for use by non-specialist

clinical staff outside normal clinical hours with a focus on timely receipt of antibiotics.

Readmission with pneumonia is common and associated with significant mortality. Rates of re-consultation in primary care following admission with CAP in the UK are significant (55.9%) and highest within 7 days of discharge (205). Reasons for re-consultation are not fully understood but could include failure of initial treatment, secondary exacerbation of co-morbid disease and decompensation of social systems on discharge. Repeat antibiotic prescription was high at 31.1% with important implications for antimicrobial stewardship (205). The combined usage of primary care and hospital services represents a significant burden of morbidity following discharge for this common condition and highlights the need for strategies to reduce this. Given the significant contribution of respiratory disease to adverse outcomes, simple measures to target established risk factors such as nicotine addiction and inappropriate inhaled corticosteroid (ICS) use are warranted (206-208). In the UK, the BTS National Smoking Cessation Audit 2019 reported that only 1 in 2 current smokers were asked if they would like help to quit and 1 in 8 were referred to smoking cessation services (209). This suggests ongoing need for improvement in this area. Mirroring recommendations made in established guidelines on the management of patients with chronic respiratory disease, review of immunomodulatory medication including ICS use should take place at discharge (210). Vaccination against pneumococcal pneumonia, influenza and COVID-19 are key public health initiatives to decrease acute respiratory infections at a population level. Review of vaccination status prior to discharge can simply identify unvaccinated individuals who are eligible for vaccination in this high-risk group with subsequent recommendations communicated to both the patient and primary care. In a wider context, there is established evidence

of a higher incidence of cardiovascular disease following hospitalisation with pneumonia (115, 117, 118, 121). Where appropriate, investigation for and optimisation of cardiovascular co-morbidity should be considered prior to discharge. When combined, these simple established health interventions form a holistic checklist that could be utilised at the point of discharge.

Prior to the COVID-19 pandemic, there was established evidence of substantial morbidity in patients hospitalised with CAP reported up to 6 weeks post-discharge (211). Rates of symptom persistence, anxiety, functional impairment and healthcare re-consultation were high with marked impact of quality of life (212). Although recognised, this syndrome was poorly described. The COVID-19 pandemic has led to widespread recognition of a post-COVID syndrome or “long COVID” (213). This term encompasses both ongoing symptomatic COVID-19 infection (4-12 weeks post onset) and those with post-COVID-19 syndrome (12 weeks or more). Symptoms include chronic cough, fatigue, dyspnoea, pain and cognitive impairment (214). In the UK, a large multicentre observational study of adults discharged following admission with COVID-19 reported that only 28.8% of the participants described themselves as ‘fully recovered’ at a median follow-up of 5 months and 20% reported a new disability (215). In response, guidelines for the management of the long-term effects of COVID-19 and innovative programmes to support discharge in COVID-19 patients were developed (213). Some parallels exist between the syndrome of impaired recovery following admission with CAP and long COVID however the extent of these is not examined as yet. As the dominance of SARS-CoV-2 decreases and the spectrum of pathogens causing CAP diversifies again, it is important that research into patients with CAP caused by conventional respiratory pathogens is conducted to meet this previously recognised, but now highlighted, need.

8.1.3 Further Work

Further work building on themes explored in this thesis regarding healthcare outcomes in CAP are suggested below:

1. A multicentre prospective observational study to examine the long-term effects of pneumonia on adults following discharge. This study should assess recovery over several domains: physiological, functional, cognitive and psychosocial. It should incorporate PROMS to fully assess the impact of disease on the patient. It might run as a stand-alone study or, more pragmatically, as a parallel arm in an established COVID-19 follow-up study allowing comparison between the two cohorts. This is increasingly important as the dominance of SARS-CoV-2 pathogen decreases and the diverse spectrum of pathogens causing CAP return.

2. An observational cohort study to assess healthcare utilisation and examine the reasons for re-consultation and readmission. The aims of this study would be to classify reasons for healthcare utilisation post discharge, identify those at risk and guide development of targeted supportive discharge measures. A secondary aim would be to provide information on antibiotic usage post discharge which has important implications in antimicrobial stewardship. It should focus on short term health utilisation only (within 2- 4 weeks of discharge). To avoid acquisition bias associated with prospective observational follow-up studies, national audit data linked to primary healthcare data could be utilised to capture both those who do and do not re-consult. Running parallel to audit data collection, a patient survey at 2- and 4-weeks post discharge would identify healthcare seeking behaviour outside that recorded in primary or secondary care databases (visits to pharmacists or private healthcare providers).

3. A holistic discharge checklist including established healthcare interventions as described above should be developed and tested. A multicentre prospective observational study examining healthcare utilisation following discharge in individuals at hospitals before and after the implementation of the checklist should then be performed. Secondary outcomes might include repeat antibiotic prescription, short term exacerbation of co-morbid disease and patient reported outcome measures.

8.1.3.1 Recommendations for future National CAP Audits

1) A retrospective cohort study in the US suggested that using the CURB-65 elements as continuous and weighted data improved prediction of severity and 30-day mortality (216). Future national BTS CAP audits should consider collecting continuous rather than binary data points for the CURB-65 variables to improve accuracy of severity scoring and result interpretation.
2) Continuous year-round national audit data collection, similar to that achieved by the National Asthma and COPD audit programme (217), would enable hospitals to monitor and improve quality of care annually. It would allow demographic, process of care and outcome data to be compared across seasons and peaks in circulating respiratory pathogens.

8.2 Variation

8.2.1 Key Points

This thesis examines both established evidence of variation in CAP and variation in outcomes across the UK. Review of existing literature found consistent evidence of moderate quality for variation in LOS and process of care measures but not for in-patient mortality or hospital re-admission rates. Evidence linking variation in outcomes with variation in process of care measures was limited due to a lack of relevant studies. In agreement with these findings, analysis of variation in BTS audit data found inter-Trust variation in 30-day mortality and readmission was low. Greater variation in length of stay and process of care measures were observed. A high proportion of the observed variation in all outcome measures examined could be attributed to chance. No significant association between outlier status for mortality and variation in process of care measures was observed.

8.2.2 Clinical Implications:

Future studies assessing the impact of healthcare variation in clinically important outcomes for patients hospitalised with pneumonia require large granular datasets comprising multiple subunits (at least 10, preferably >20) each with representative patient samples. Robust and consistent statistical methodology to identify outlying institutions that allows for natural variation should be used. The Spiegaelhalter method, increasingly used in the UK for national audit reports, is one suggested method (101, 218).

Focus on potential causes of variation in length of stay, where the greatest variation was observed, and identification of potential strategies to reduce unwarranted variation is advised. Datasets should include detailed outcome data linked at a patient level and a measure of socioeconomic

status. Ranking of outcome measures should be avoided unless coupled with a valid assessment of rankability of the outcome measure utilised. None of the outcome measures commonly used currently were found to be suitable for this. Limited evidence for an association between variation in process of care measures and variation in outcome measures was observed, despite the use of large granular datasets. The magnitude of variation in single POC measures may be too small to impact on outcome and therefore have limited utility.

Since the inception of this thesis, the COVID-19 pandemic has changed the landscape of respiratory infection. As a novel virus and disease, there was no established evidence base to guide treatment of patients with COVID during the early pandemic stages. Greater variation in practice exists where evidence for effective treatment is lacking (45). In the UK, randomised controlled trials such as RECOVERY and REMAP-CAP have provided evidence regarding drug therapy and informed practice-based guidelines (219-223). However, many uncertainties remain around management of patients hospitalised with COVID-19, particularly where treatment strategies are not amenable to inclusion in RCTs and more susceptible to local resources (224). Uncertainty regarding ventilation strategies and has led to variation in approaches to invasive and non-invasive ventilation (225). Discharge support has varied between hospitals and some have developed ‘virtual wards’ to allow management of patients at home (226). Where ongoing uncertainty remains due to lack of evidence-based medicine, treatment and discharge pathways are likely to vary still over coming years. The methodology described and lessons derived from this thesis have utility when identifying outlier Trusts for COVID-19 outcomes. Indeed, this method was used to assess inter-Trust variation in mortality during the first wave of the COVID-19 pandemic in the UK (March – May 2020) (227). Ongoing assessment of adverse healthcare

outcomes is therefore required to identify outlying Trusts, drive quality improvement at poorly performing institutions and identify centres with transferable good practice pathways.

8.2.3 Further Work

Development of a platform using real time data analysis and the methodology described would allow temporal variation analysis and monitoring of Trust performance over time. This would identify outliers in a timely manner allowing prompt alerting of Trusts and local performance review, driving quality improvement at these institutions. Both CAP and COVID-19 subgroups could be examined. Continuous national audit data collection, such as that seen in other national audits, would be required (217). Where possible, data from routinely collected datasets or strategies allowing automated data collection should be used to reduce burden on clinical sites and reduce the proportion of missing data.

8.3 PPV23 Vaccination

8.3.1 Key Findings

In the setting of an established national childhood PCV13 vaccination programme, PPV23 vaccination in clinical at-risk patient groups and adults ≥65 years of age appears moderately effective against hospitalisation with PPV23 serotype pneumococcal pneumonia.

8.3.2 Clinical Implications

The current UK adult pneumococcal vaccine policy appropriately identifies clinical at-risk patient groups who benefit from PPV23 vaccination. However, there is a suggestion, consistent with data from other studies, that protection more than 15 years after vaccination is low (228). In many countries, the vast majority of adults who receive PPV23 vaccination do so at, or before, the age of 65 years, while the median age of adults hospitalised with CAP is around 75 years (17). This raises questions regarding the timing of adult pneumococcal vaccination and the role and value of revaccination in the context of an ageing population (229, 230). Absolute antibody levels against PPV23 vaccine serotypes decline following vaccination but persist at levels above those of vaccine naïve comparisons for up to ten years post vaccine (231, 232). As with initial immunogenic response to vaccine, duration of protection may vary with serotype; *Musher et al.* reported a return to baseline levels for serotype 3 IgG antibodies within two years of vaccination compared to up to 10 years in 7 other serotypes studied (231). Revaccination of older adults with PPV23 induces immunogenic responses similar to that of the primary vaccination; no evidence of immune hypo-responsiveness following is reported (231-237). It is well tolerated and associated with only mild self-limiting reactions lasting on average 5 days (232-234, 237). Revaccinations produces a response in older age groups; *Kawakami et al.*

demonstrated an immunogenic response to revaccination even in those over 80 years of age (235). In Japan, revaccination of older adults vaccinated over 5 years prior was recommended in 2017, however in practice revaccination rates remain very low (3.5%) (238).

As yet, minimal data on the effectiveness of PPV23 revaccination at preventing clinical disease are available with limited studies assessing clinical outcomes (232, 239). In their study of IPD in a high-risk population of Indigenous Australian adults, *Takashima et al*. reported no benefit of revaccination with PPV23 against IPD (240). No studies to date have assessed the impact of revaccination on all pneumococcal disease, including NIPP. Well conducted RCTs using clinical outcomes encompassing both IPD and NIPP to estimate the public health benefit of revaccination of older people are required, however are likely to be costly and labour intensive. Linkage of IPD national surveillance datasets to HES and GP databases might provide an alternative method for assessing the effect of revaccination but would be limited to examining IPD only. In addition, newer multivalent PCV vaccines are coming to market and may provide alternative options to consider (241, 242).

8.3.3 Further research

National respiratory infection surveillance centres providing comprehensive aetiological investigation of patients admitted with both invasive and non-invasive pneumonia, including analysis of pneumococcal serotype, are required. These centres would allow monitoring of changes in predominant serotypes in adult disease resulting from any changes in childhood pneumococcal vaccine policies. They would allow further study of viral co-infection with pneumococcal disease, particularly seasonal influenza and SARS-CoV-2. They would provide an opportunity for research to inform

public health policies including a randomised control trial examining the benefits of pneumococcal revaccination in adults 5-10 years following the initial PPV23 vaccination.

8.4 Conclusion:

This thesis describes variation in healthcare outcomes in adults admitted to hospital in the UK with all-cause CAP in reference inter-Trust variation, socio-economic deprivation and time of presentation to hospital. In addition, it demonstrates the effectiveness of PPV23 vaccination against hospitalisation with PPV23 serotype pneumococcal pneumonia in adults. Suggestions for further work include the role of repeat adult pneumococcal vaccination and a prospective study to examine the short-term effects of pneumonia on adults following discharge from hospital. The methodology used in this thesis might be used in the future to identify institutions with outlying results from routinely collected data, triggering local quality improvement initiatives.

Chapter 9 References

1. Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Le Jeune I, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax. 2009;64 Suppl 3:iii1-55.
2. Torres A, Cillóniz C, Blasi F, Chalmers JD, Gaillat J, Dartois N, et al. Burden of pneumococcal community-acquired pneumonia in adults across Europe: A literature review. Respiratory Medicine. 2018;137:6-13.
3. Millett ER, Quint JK, Smeeth L, Daniel RM, Thomas SL. Incidence of community-acquired lower respiratory tract infections and pneumonia among older adults in the United Kingdom: a population-based study. PloS one. 2013;8(9):e75131.
4. Gutiérrez F, Masiá M, Mirete C, Soldán B, Rodríguez JC, Padilla S, et al. The influence of age and gender on the population-based incidence of community-acquired pneumonia caused by different microbial pathogens. The Journal of infection. 2006;53(3):166-74.
5. Almirall J, Serra-Prat M, Bolibar I, Balasso V. Risk Factors for Community-Acquired Pneumonia in Adults: A Systematic Review of Observational Studies. Respiration; international review of thoracic diseases. 2017;94(3):299-311.
6. Myles PR, McKeever TM, Pogson Z, Smith CJ, Hubbard RB. The incidence of pneumonia using data from a computerized general practice database. Epidemiology and infection. 2009;137(5):709-16.
7. British Lung Foundation B. Pneumonia Statistics: British Lung Foundation; 2018 [Available from: https://statistics.blf.org.uk/pneumonia.
8. Ramirez JA, Wiemken TL, Peyrani P, Arnold FW, Kelley R, Mattingly WA, et al. Adults Hospitalized With Pneumonia in the United States: Incidence, Epidemiology, and Mortality. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2017;65(11):1806-12.
9. Naghavi M, Abajobir AA, Abbafati C, Abbas KM, Abd-Allah F, Abera SF, et al. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet. 2017;390(10100):1151-210.
10. British Lung Foundation B. Battle for Breath. 2016.
11. Gibson JGL, R.; Sibille, Y.; Lundback, B.; Fletcher, M. Lung health in Europe Facts and Figures 2013 [updated 2013. Available from: www.erswhitebook.org.
12. Trotter CL, Stuart JM, George R, Miller E. Increasing hospital admissions for pneumonia, England. Emerging infectious diseases. 2008;14(5):727-33.
13. Tong S, Amand C, Kieffer A, Kyaw MH. Trends in healthcare utilization and costs associated with pneumonia in the United States during 2008-2014. BMC health services research. 2018;18(1):715-.
14. Shoar S, Musher DM. Etiology of community-acquired pneumonia in adults: a systematic review. Pneumonia. 2020;12(1):11.
15. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax. 2012;67(1):71-9.
16. Daniel P, Woodhead M, Welham S, McKeever TM, Lim WS. Mortality reduction in adult community-acquired pneumonia in the UK (2009-2014): results from the British Thoracic Society audit programme. Thorax. 2016;71(11):1061-3.
17. British Thoracic Society B, Lawrence H, Lim WS. National Audit Report: Adult Community Acquired Pneumonia Audit 2018-2019. Online; 2019.
18. NICE. Pneumonia in adults: diagnosis and management 2014 [Available from: https://www.nice.org.uk/guidance/cg191.
19. Project HcaU. Most Common Diagnoses for Inpatient Stays 2018 [Available from: https://www.hcup-us.ahrq.gov/faststats/NationalDiagnosesServlet.
20. Guest JF, Morris A. Community-acquired pneumonia: the annual cost to the National Health Service in the UK. The European respiratory journal. 1997;10(7):1530-4.

21. Improvement NEaN. Same Day Emergency Care CQUIN 2019 [Available from: https://www.england.nhs.uk/wp-content/uploads/2020/08/SDEC_FAQs_230819.pdf.
22. Friebel R, Hauck K, Aylin P, Steventon A. National trends in emergency readmission rates: a longitudinal analysis of administrative data for England between 2006 and 2016. BMJ open. 2018;8(3):e020325-e.
23. Capelastegui A, España Yandiola PP, Quintana JM, Bilbao A, Diez R, Pascual S, et al. Predictors of short-term rehospitalization following discharge of patients hospitalized with community-acquired pneumonia. Chest. 2009;136(4):1079-85.
24. Jang JG, Ahn JH. Reasons and Risk Factors for Readmission Following Hospitalization for Community-acquired Pneumonia in South Korea. Tuberc Respir Dis (Seoul). 2020;83(2):147-56.
25. Jasti H, Mortensen EM, Obrosky DS, Kapoor WN, Fine MJ. Causes and Risk Factors for Rehospitalization of Patients Hospitalized with Community-Acquired Pneumonia. Clinical Infectious Diseases. 2008;46(4):550-6.
26. Adamuz J, Viasus D, Campreciós-Rodríguez P, Cañavate-Jurado O, Jiménez-Martínez E, Isla P, et al. A prospective cohort study of healthcare visits and rehospitalizations after discharge of patients with community-acquired pneumonia. Respirology (Carlton, Vic). 2011;16(7):1119-26.
27. Taylor JK, Fleming GB, Singanayagam A, Hill AT, Chalmers JD. Risk factors for aspiration in community-acquired pneumonia: analysis of a hospitalized UK cohort. The American journal of medicine. 2013;126(11):995-1001.
28. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003;58(5):377-82.
29. Storms AD, Chen J, Jackson LA, Nordin JD, Naleway AL, Glanz JM, et al. Rates and risk factors associated with hospitalization for pneumonia with ICU admission among adults. BMC pulmonary medicine. 2017;17(1):208.
30. Gearhart AM, Furmanek S, English C, Ramirez J, Cavallazzi R. Predicting the need for ICU admission in community-acquired pneumonia. Respir Med. 2019;155:61-5.
31. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, et al. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. The New England journal of medicine. 2015;373(5):415-27.
32. Chalmers JD, Mandal P, Singanayagam A, Akram AR, Choudhury G, Short PM, et al. Severity assessment tools to guide ICU admission in community-acquired pneumonia: systematic review and meta-analysis. Intensive care medicine. 2011;37(9):1409-20.
33. Niederman MS. Pneumonia: Considerations for the Critically Ill Patient. Critical care medicine. 2008:867-83.
34. Society BT. Annotated BTS Guideline for the management of CAP in adults (2009)

Summary of recommendations. 2015.
35. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. American journal of respiratory and critical care medicine. 2019;200(7):e45-e67.
36. NICE. Pneumonia (community-acquired): antimicrobial prescribing2019; (NICE guideline [NG138]). Available from: https://www.nice.org.uk/guidance/ng138.
37. Lim WS, Lewis S, Macfarlane JT. Severity prediction rules in community acquired pneumonia: a validation study. Thorax. 2000;55(3):219-23.
38. Chalmers JD, Singanayagam A, Akram AR, Mandal P, Short PM, Choudhury G, et al. Severity assessment tools for predicting mortality in hospitalised patients with community-acquired pneumonia. Systematic review and meta-analysis. Thorax. 2010;65(10):878-83.

39. Daniel P, Rodrigo C, McKeever TM, Woodhead M, Welham S, Lim WS. Time to first antibiotic and mortality in adults hospitalised with community-acquired pneumonia: a matched-propensity analysis. Thorax. 2016;71(6):568-70.
40. Claessens YE, Debray MP, Tubach F, Brun AL, Rammaert B, Hausfater P, et al. Early Chest Computed Tomography Scan to Assist Diagnosis and Guide Treatment Decision for Suspected Community-acquired Pneumonia. American journal of respiratory and critical care medicine. 2015;192(8):974-82.
41. Prendki V, Scheffler M, Huttner B, Garin N, Herrmann F, Janssens J-P, et al. Low-dose computed tomography for the diagnosis of pneumonia in elderly patients: a prospective, interventional cohort study. The European respiratory journal. 2018;51(5):1702375.
42. Upchurch CP, Grijalva CG, Wunderink RG, Williams DJ, Waterer GW, Anderson EJ, et al. Community-Acquired Pneumonia Visualized on CT Scans but Not Chest Radiographs: Pathogens, Severity, and Clinical Outcomes. Chest. 2018;153(3):601-10.
43. Strøm JJ, Haugen PS, Hansen MP, Graumann O, Jensen MBB, Aakjær Andersen C. Accuracy of lung ultrasonography in the hands of non-imaging specialists to diagnose and assess the severity of community-acquired pneumonia in adults: a systematic review. BMJ open. 2020;10(6):e036067.
44. Cripps M. What do we mean by 'variation' and when is it 'unwarranted'? NHS RightCare2017 [Available from: https://www.england.nhs.uk/rightcare/2017/01/04/matthew-cripps-3/.
45. Wennberg JE. Tracking Medicine: A Researcher's Quest to Understand Health Care. New York: Oxford University Press; 2010 2 Dec 2010.
46. Glover JA. The Incidence of Tonsillectomy in School Children: (Section of Epidemiology and State Medicine). Proc R Soc Med. 1938;31(10):1219-36.
47. Project DA. The Dartmouth Atlas of Health Care 2020 [Available from: https://www.dartmouthatlas.org/.
48. Australian Commission on Safety and Quality in Health Care NHPA. Australian atlas of healthcare variation. 2018 [Available from: https://www.safetyandquality.gov.au/atlas/atlas-2017/.
49. NHS RC. NHS Atlas of Variation in Healthcare for People with Respiratory Disease 2012 [updated September 2012. Available from: https://fingertips.phe.org.uk/profile/atlas-of-variation.
50. Bernal-Delgado E, García-Armesto S, Peiró S. Atlas of Variations in Medical Practice in Spain: the Spanish National Health Service under scrutiny. Health Policy. 2014;114(1):15-30.
51. OECD. Geographic Variation in Health Care. OECD; September 2014 September 2014.
52. VPM VelPM. Atases 2020 [Available from: https://www.atlasvpm.org/en/atlases/.
53. Appleby JA. Variations in Health Care; The good, the bad and the inexplicable 2011 [updated 2011. Available from: http://www.kingsfund.org.uk/publications/healthcare_variation.html.
54. Suleman M, Clark MP, Goldacre M, Burton M. Exploring the variation in paediatric tonsillectomy rates between English regions: a 5-year NHS and independent sector data analysis. Clin Otolaryngol. 2010;35(2):111-7.
55. Gray WK, Takhar AS, Navaratnam AV, Day J, Swart M, Snowden C, et al. Safety of day-case paediatric tonsillectomy in England: an analysis of administrative data for the Getting It Right First Time programme. Anaesthesia. 2022;77(3):277-85.
56. RightCare N. Respiratory Atlas 2019 [Available from: https://www.england.nhs.uk/rightcare/products/atlas/.
57. Torres A, Niederman MS, Chastre J, Ewig S, Fernandez-Vandellos P, Hanberger H, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care

Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT). The European respiratory journal. 2017;50(3).
58. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1736-88.
59. Austrian R. The pneumococcus at the millennium: not down, not out. The Journal of infectious diseases. 1999;179 Suppl 2:S338-41.
60. Woodhead M. Community-acquired pneumonia in Europe: causative pathogens and resistance patterns. Eur Respir J Suppl. 2002;36:20s-7s.
61. Weichselbaum A. Ueber die Aetiologie der acuten Lungen-und Rippenfellentzundungen. Mede Jahrb. 1886;1:484-554.
62. Austrian R. A brief history of pneumococcal vaccines. Drugs & aging. 1999;15 Suppl 1:1-10.
63. Hyams C, Camberlein E, Cohen JM, Bax K, Brown JS. The Streptococcus pneumoniae capsule inhibits complement activity and neutrophil phagocytosis by multiple mechanisms. Infect Immun. 2010;78(2):704-15.
64. Cooper G, Rosenstein C, Walter A, Peizer L. THE FURTHER SEPARATION OF TYPES AMONG THE PNEUMOCOCCI HITHERTO INCLUDED IN GROUP IV AND THE DEVELOPMENT OF THERAPEUTIC ANTISERA FOR THESE TYPES. J Exp Med. 1932;55(4):531-54.
65. Geno KA, Gilbert GL, Song JY, Skovsted IC, Klugman KP, Jones C, et al. Pneumococcal Capsules and Their Types: Past, Present, and Future. Clinical microbiology reviews. 2015;28(3):871-99.
66. Public Health England P. Immunisation against infectious disease - The Green Book. Chapter 25: Pneumococcal 2018 [Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/674074/GB_Chapter_25_Pneumococcal_V7_0.pdf.
67. Clutterbuck EA, Lazarus R, Yu L-M, Bowman J, Bateman EAL, Diggle L, et al. Pneumococcal Conjugate and Plain Polysaccharide Vaccines Have Divergent Effects on Antigen-Specific B Cells. The Journal of infectious diseases. 2012;205(9):1408-16.
68. Farmaki PF, Chini MC, Mangafas NM, Tzanoudaki MT, Piperi CP, Lazanas MZ, et al. Immunogenicity and Immunological Memory Induced by the 13-Valent Pneumococcal Conjugate Followed by the 23-Valent Polysaccharide Vaccine in HIV-Infected Adults. The Journal of infectious diseases. 2018;218(1):26-34.
69. WHO WHO. Duration of Protection and Revaccination. 2003.
70. Public Health England P. Pneumococcal Polysacchardie Vaccine (PPV) coverage report, England, April 2017 to March 2018. 2018 27 July 2018. Report No.: Number 27.
71. Daniel P, Bewick T, Welham S, McKeever TM, Lim WS. Adults miscoded and misdiagnosed as having pneumonia: results from the British Thoracic Society pneumonia audit. Thorax. 2017;72(4):376-9.
72. Lilford R, Mohammed MA, Spiegelhalter D, Thomson R. Use and misuse of process and outcome data in managing performance of acute medical care: avoiding institutional stigma. Lancet. 2004;363(9415):1147-54.
73. Adab P, Rouse AM, Mohammed MA, Marshall T. Performance league tables: the NHS deserves better. BMJ (Clinical research ed). 2002;324(7329):95-8.
74. Burns LR, Wholey DR. The effects of patient, hospital, and physician characteristics on length of stay and mortality. Med Care. 1991;29(3):251-71.
75. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ (Clinical research ed). 2009;339:b2535.
76. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clinical

infectious diseases : an official publication of the Infectious Diseases Society of America. 2007;44 Suppl 2:S27-72.
77. Lim WS, Rodrigo C, Turner AM, Welham S, Calvert JM, British Thoracic S. British Thoracic Society community-acquired pneumonia care bundle: results of a national implementation project. Thorax. 2016;71(3):288-90.
78. Fine MJ, Singer DE, Phelps AL, Hanusa BH, Kapoor WN. Differences in length of hospital stay in patients with community-acquired pneumonia: a prospective four-hospital study. Med Care. 1993;31(4):371-80.
79. Aelvoet W, Terryn N, Blommaert A, Molenberghs G, Hens N, De Smet F, et al. Community-acquired pneumonia (CAP) hospitalizations and deaths: is there a role for quality improvement through inter-hospital comparisons? International journal for quality in health care : journal of the International Society for Quality in Health Care. 2016;28(1):22-32.
80. Arnold FW, Wiemken TL, Peyrani P, Ramirez JA, Brock GN, authors C. Mortality differences among hospitalized patients with community-acquired pneumonia in three world regions: results from the Community-Acquired Pneumonia Organization (CAPO) International Cohort Study. Respiratory medicine. 2013;107(7):1101-11.
81. Blasi F, Garau J, Medina J, Avila M, McBride K, Ostermann H, et al. Current management of patients hospitalized with community-acquired pneumonia across Europe: outcomes from REACH. Respiratory research. 2013;14:44.
82. Cabre M, Bolivar I, Pera G, Pallares R, Pneumonia Study Collaborative G. Factors influencing length of hospital stay in community-acquired pneumonia: a study in 27 community hospitals. Epidemiology and infection. 2004;132(5):821-9.
83. Capelastegui A, Espana PP, Quintana JM, Gorordo I, Gallardo MS, Idoiaga I, et al. Management of community-acquired pneumonia and secular trends at different hospitals. Respiratory medicine. 2005;99(3):268-78.
84. Dedier J, Singer DE, Chang Y, Moore M, Atlas SJ. Processes of care, illness severity, and outcomes in the management of community-acquired pneumonia at academic hospitals. Arch Intern Med. 2001;161(17):2099-104.
85. Feagan BG, Marrie TJ, Lau CY, Wheeler SL, Wong CJ, Vandervoort MK. Treatment and outcomes of community-acquired pneumonia at Canadian hospitals. CMAJ. 2000;162(10):1415-20.
86. Garau J, Baquero F, Perez-Trallero E, Perez JL, Martin-Sanchez AM, Garcia-Rey C, et al. Factors impacting on length of stay and mortality of community-acquired pneumonia. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2008;14(4):322-9.
87. Gilbert K, Gleason PP, Singer DE, Marrie TJ, Coley CM, Obrosky DS, et al. Variations in antimicrobial use and cost in more than 2,000 patients with community-acquired pneumonia. The American journal of medicine. 1998;104(1):17-27.
88. Hedlund J, Ortqvist A, Ahlqvist T, Augustinsson A, Beckman H, Blanck C, et al. Management of patients with community-acquired pneumonia treated in hospital in Sweden. Scandinavian journal of infectious diseases. 2002;34(12):887-92.
89. Iroezindu MO, Isiguzo GC, Chima EI, Mbata GC, Onyedibe KI, Onyedum CC, et al. Predictors of in-hospital mortality and length of stay in community-acquired pneumonia: a 5-year multi-centre case control study of adults in a developing country. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2016;110(8):445-55.
90. Laing R, Coles C, Chambers S, Frampton C, Jennings L, Karalus N, et al. Community-acquired pneumonia: influence of management practices on length of hospital stay. Internal medicine journal. 2004;34(3):91-7.
91. Lave JR, Fine MJ, Sankey SS, Hanusa BH, Weissfeld LA, Kapoor WN. Hospitalized pneumonia. Outcomes, treatment patterns, and costs in urban and rural areas. J Gen Intern Med. 1996;11(7):415-21.
92. Malone DC, Shaban HM. Adherence to ATS guidelines for hospitalized patients with community-acquired pneumonia. Ann Pharmacother. 2001;35(10):1180-5.

93. McCormick D, Fine MJ, Coley CM, Marrie TJ, Lave JR, Obrosky DS, et al. Variation in length of hospital stay in patients with community-acquired pneumonia: are shorter stays associated with worse medical outcomes? The American journal of medicine. 1999;107(1):5-12.
94. Menendez R, Cremades MJ, Martinez-Moragon E, Soler JJ, Reyes S, Perpina M. Duration of length of stay in pneumonia: influence of clinical factors and hospital type. The European respiratory journal. 2003;22(4):643-8.
95. Remond MGW, Ralph AP, Brady SJ, Martin J, Tikoft E, Maguire GP. Community-acquired pneumonia in the central desert and north-western tropics of Australia. Internal medicine journal. 2010;40(1):37-44.
96. Reyes Calzada S, Martinez Tomas R, Cremades Romero MJ, Martinez Moragon E, Soler Cataluna JJ, Menendez Villanueva R. Empiric treatment in hospitalized community-acquired pneumonia. Impact on mortality, length of stay and re-admission. Respiratory medicine. 2007;101(9):1909-15.
97. Schouten JA, Hulscher ME, Kullberg B-J, Cox A, Gyssens IC, van der Meer JW, et al. Understanding variation in quality of antibiotic use for community-acquired pneumonia: effect of patient, professional and hospital factors. The Journal of antimicrobial chemotherapy. 2005;56(3):575-82.
98. Sow O, Frechet M, Diallo AA, Soumah S, Conde MK, Diot P, et al. Community acquired pneumonia in adults: a study comparing clinical features and outcome in Africa (Republic of Guinea) and Europe (France). Thorax. 1996;51(4):385-8.
99. Klausen HH, Petersen J, Lindhardt T, Bandholm T, Hendriksen C, Kehlet H, et al. Outcomes in elderly Danish citizens admitted with community-acquired pneumonia. Regional differencties, in a public healthcare system. Respir Med. 2012;106(12):1778-87.
100. Newton JN, Briggs AD, Murray CJ, Dicker D, Foreman KJ, Wang H, et al. Changes in health in England, with analysis by English regions and areas of deprivation, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;386(10010):2257-74.
101. Royal College Physicians R. National Lung Cancer Audit annual report 2017. Royal College Physicians, London; 2018.
102. Austin PC, Ceyisakar IE, Steyerberg EW, Lingsma HF, Marang-van de Mheen PJ. Ranking hospital performance based on individual indicators: can we increase reliability by creating composite indicators? BMC Medical Research Methodology. 2019;19(1):131.
103. van Dishoeck AM, Lingsma HF, Mackenbach JP, Steyerberg EW. Random variation and rankability of hospitals using outcome indicators. BMJ Qual Saf. 2011;20(10):869-74.
104. Nsutebu EF, Ibarz-Pavon AB, Kanwar E, Prospero N, French N, McGrath C. Advancing quality in sepsis management: a large-scale programme for improving sepsis recognition and management in the North West region of England. Postgraduate medical journal. 2018;94(1114):463-8.
105. van den Bosch CM, Hulscher ME, Akkermans RP, Wille J, Geerlings SE, Prins JM. Appropriate antibiotic use reduces length of hospital stay. J Antimicrob Chemother. 2017;72(3):923-32.
106. Metersky ML, Waterer G, Nsa W, Bratzler DW. Predictors of in-hospital vs postdischarge mortality in pneumonia. Chest. 2012;142(2):476-81.
107. Prescott HC, Sjoding MW, Iwashyna TJ. Diagnoses of early and late readmissions after hospitalization for pneumonia. A systematic review. Annals of the American Thoracic Society. 2014;11(7):1091-100.
108. Digital N. Hospital Episode Statistics Data Dictionary 2020 [Admitted patient care, critical care and HES-ONS linked mortality data]. Available from: https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics/hospital-episode-statistics-data-dictionary.
109. World Health Organization W. ICD-10 2019 [10th Revision:[International Statistical Classification of Diseases and Related Health Problems]. Available from: https://icd.who.int/browse10/2019/en.

110. Steventon A, Deeney S, Friebel R, Gardner T, Thorlby R. Emergency hospital admissions in England: which may be avoidable and how? : The Health Foundation; 2018 May 2018.
111. Shiue I, McMeekin P, Price C. Retrospective observational study of emergency admission, readmission and the 'weekend effect'. BMJ open. 2017;7(3):e012493.
112. Digital N. Hospital Admitted Patient Care Activity, 2016-17. Online; 2017 3/10/2017.
113. Mortensen EM, Coley CM, Singer DE, Marrie TJ, Obrosky DS, Kapoor WN, et al. Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. Arch Intern Med. 2002;162(9):1059-64.
114. Corrales-Medina VF, Suh KN, Rose G, Chirinos JA, Doucette S, Cameron DW, et al. Cardiac complications in patients with community-acquired pneumonia: a systematic review and meta-analysis of observational studies. PLoS medicine. 2011;8(6):e1001048.
115. Violi F, Cangemi R, Falcone M, Taliani G, Pieralli F, Vannucchi V, et al. Cardiovascular Complications and Short-term Mortality Risk in Community-Acquired Pneumonia. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2017;64(11):1486-93.
116. Asaria P, Elliott P, Douglass M, Obermeyer Z, Soljak M, Majeed A, et al. Acute myocardial infarction hospital admissions and deaths in England: a national follow-back and follow-forward record-linkage study. Lancet Public Health. 2017;2(4):e191-e201.
117. Perry TW, Pugh MJV, Waterer GW, Nakashima B, Orihuela CJ, Copeland LA, et al. Incidence of cardiovascular events after hospital admission for pneumonia. The American journal of medicine. 2011;124(3):244-51.
118. Griffin AT, Wiemken TL, Arnold FW. Risk factors for cardiovascular events in hospitalized patients with community-acquired pneumonia. International Journal of Infectious Diseases. 2013;17(12):e1125-e9.
119. Corrales-Medina VF, Alvarez KN, Weissfeld LA, Angus DC, Chirinos JA, Chang CC, et al. Association between hospitalization for pneumonia and subsequent risk of cardiovascular disease. Jama. 2015;313(3):264-74.
120. Reyes LF, Restrepo MI, Hinojosa CA, Soni NJ, Anzueto A, Babu BL, et al. Severe Pneumococcal Pneumonia Causes Acute Cardiac Toxicity and Subsequent Cardiac Remodeling. American journal of respiratory and critical care medicine. 2017;196(5):609-20.
121. Rae N, Finch S, Chalmers JD. Cardiovascular disease as a complication of community-acquired pneumonia. Curr Opin Pulm Med. 2016;22(3):212-8.
122. Herbert A, Wijlaars L, Zylbersztejn A, Cromwell D, Hardelid P. Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). International journal of epidemiology. 2017;46(4):1093-i.
123. CAPITA. Payment by results data assurance framework: key findings from the 2012/13 programme. 2013.
124. CAPITA. The quality of clinical coding in the NHS. 2014.
125. Burns EM, Rigby E, Mamidanna R, Bottle A, Aylin P, Ziprin P, et al. Systematic review of discharge coding accuracy. Journal of public health (Oxford, England). 2012;34(1):138-48.
126. Hagger-Johnson G, Harron K, Fleming T, Gilbert R, Goldstein H, Landy R, et al. Data linkage errors in hospital administrative data when applying a pseudonymisation algorithm to paediatric intensive care records. BMJ open. 2015;5(8):e008118.
127. Mathur R, Bhaskaran K, Chaturvedi N, Leon DA, vanStaa T, Grundy E, et al. Completeness and usability of ethnicity data in UK-based primary care and hospital databases. Journal of public health (Oxford, England). 2014;36(4):684-92.
128. Daniel P, Bewick T, McKeever TM, Roberts M, Ashton D, Smith D, et al. Healthcare reconsultation in working-age adults following hospitalisation for community-acquired pneumonia. Clin Med (Lond). 2018;18(1):41-6.

129. Daniel P, Bewick, T., Welham, S., Lim, WS. Adult Community Acquired Pneumonia Audit Report (National Audit Period: 1 December 2014 to 31 January 2015). British Thoracic Society; 2015.
130. Textor J, van der Zander B, Gilthorpe MS, Liśkiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. International journal of epidemiology. 2017;45(6):1887-94.
131. Spiegelhalter DJ. Funnel plots for comparing institutional performance. Statistics in medicine. 2005;24(8):1185-202.
132. Lingsma HF, Eijkemans MJC, Steyerberg EW. Incorporating natural variation into IVF clinic league tables: The Expected Rank. BMC Medical Research Methodology. 2009;9(1):53.
133. Hofstede SN, Ceyisakar IE, Lingsma HF, Kringos DS, Marang-van de Mheen PJ. Ranking hospitals: do we gain reliability by using composite rather than individual indicators? BMJ Qual Saf. 2019;28(2):94-102.
134. Goldstein H, Spiegelhalter DJ. League Tables and Their Limitations: Statistical Issues in Comparisons of Institutional Performance. Journal of the Royal Statistical Society Series A (Statistics in Society). 1996;159(3):385-443.
135. Lawrence H, Lim WS, McKeever TM. Variation in clinical outcomes and process of care measures in community acquired pneumonia: a systematic review. Pneumonia (Nathan). 2020;12:10.
136. McMullan R, Silke B, Bennett K, Callachand S. Resource utilisation, length of hospital stay, and pattern of investigation during acute medical hospital admission. Postgraduate medical journal. 2004;80(939):23-6.
137. Hadfield J, Bennett L. Determining best outcomes from community-acquired pneumonia and how to achieve them. Respirology (Carlton, Vic). 2018;23(2):138-47.
138. Improvement NEaN. CCG Indicator Specifications for 2019-2020. 2019.
139. Lingsma HF, Bottle A, Middleton S, Kievit J, Steyerberg EW, Marang-van de Mheen PJ. Evaluation of hospital outcomes: the relation between length-of-stay, readmission, and mortality in a large international administrative database. BMC Health Serv Res. 2018;18(1):116.
140. Wathne JS, Harthug S, Kleppe LKS, Blix HS, Nilsen RM, Charani E, et al. The association between adherence to national antibiotic guidelines and mortality, readmission and length of stay in hospital inpatients: results from a Norwegian multicentre, observational cohort study. Antimicrob Resist Infect Control. 2019;8:63.
141. Arnold FW, LaJoie AS, Brock GN, Peyrani P, Rello J, Menéndez R, et al. Improving outcomes in elderly patients with community-acquired pneumonia by adhering to national guidelines: Community-Acquired Pneumonia Organization International cohort study results. Arch Intern Med. 2009;169(16):1515-24.
142. Schuts EC, Hulscher M, Mouton JW, Verduin CM, Stuart J, Overdiek H, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. The Lancet Infectious diseases. 2016;16(7):847-56.
143. Chalmers JD, Singanayagam A, Akram AR, Choudhury G, Mandal P, Hill AT. Safety and efficacy of CURB65-guided antibiotic therapy in community-acquired pneumonia. J Antimicrob Chemother. 2011;66(2):416-23.
144. Almatar MA, Peterson GM, Thompson A, McKenzie DS, Anderson TL. Community-acquired pneumonia: why aren't national antibiotic guidelines followed? Int J Clin Pract. 2015;69(2):259-66.
145. Trent SA, Jarou ZJ, Havranek EP, Ginde AA, Haukoos JS. Variation in Emergency Department Adherence to Treatment Guidelines for Inpatient Pneumonia and Sepsis: A Retrospective Cohort Study. Acad Emerg Med. 2019;26(8):908-20.
146. Mohammed MA, Deeks JJ, Girling A, Rudge G, Carmalt M, Stevens AJ, et al. Evidence of methodological bias in hospital standardised mortality ratios: retrospective database study of English hospitals. BMJ (Clinical research ed). 2009;338:b780.

147. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. The Cochrane database of systematic reviews. 2013(1):Cd000422.
148. Office for National Statistics O. Deaths involving COVID-19 by local area and socioeconomic deprivation: deaths occurring between 1 March and 17 April 2020. Online; 2020 1/05/2020.
149. Wiemken TL, Carrico RM, Furmanek SP, Guinn BE, Mattingly WA, Peyrani P, et al. Socioeconomic Position and the Incidence, Severity, and Clinical Outcomes of Hospitalized Patients With Community-Acquired Pneumonia. Public Health Rep. 2020;135(3):364-71.
150. Tools N. IMD tool: University of Oxford; [Available from: https://tools.npeu.ox.ac.uk/imd/.
151. Jordan R, Verlander N, Olowokure B, Hawker JI. Age, sex, material deprivation and respiratory mortality. Respir Med. 2006;100(7):1282-5.
152. Huisman M, Kunst AE, Andersen O, Bopp M, Borgan JK, Borrell C, et al. Socioeconomic inequalities in mortality among elderly people in 11 European populations. J Epidemiol Community Health. 2004;58(6):468-75.
153. Cournane S, Byrne D, Conway R, O'Riordan D, Coveney S, Silke B. Social deprivation and hospital admission rates, length of stay and readmissions in emergency medical admissions. European journal of internal medicine. 2015;26(10):766-71.
154. Marmot MGA, J ; Boyce, T; Goldblatt, P; Morrison, J. Build back fairer: The COVID-19 Marmot Review. The Health Foundation; 2020.
155. Bell CM, Redelmeier DA. Mortality among patients admitted to hospitals on weekends as compared with weekdays. The New England journal of medicine. 2001;345(9):663-8.
156. Freemantle N, Richardson M, Wood J, Ray D, Khosla S, Shahian D, et al. Weekend hospitalization and additional risk of death: an analysis of inpatient data. J R Soc Med. 2012;105(2):74-84.
157. Han L, Sutton M, Clough S, Warner R, Doran T. Impact of out-of-hours admission on patient mortality: longitudinal analysis in a tertiary acute hospital. BMJ Qual Saf. 2018;27(6):445-54.
158. Sun J, Girling AJ, Aldridge C, Evison F, Beet C, Boyal A, et al. Sicker patients account for the weekend mortality effect among adult emergency admissions to a large hospital trust. BMJ Qual Saf. 2019;28(3):223-30.
159. Walker AS, Mason A, Quan TP, Fawcett NJ, Watkinson P, Llewelyn M, et al. Mortality risks associated with emergency admissions during weekends and public holidays: an analysis of electronic health records. Lancet. 2017;390(10089):62-72.
160. Freemantle N, Ray D, McNulty D, Rosser D, Bennett S, Keogh BE, et al. Increased mortality associated with weekend hospital admission: a case for expanded seven day services? BMJ (Clinical research ed). 2015;351:h4596.
161. Aldridge C, Bion J, Boyal A, Chen YF, Clancy M, Evans T, et al. Weekend specialist intensity and admission mortality in acute hospital trusts in England: a cross-sectional study. Lancet. 2016;388(10040):178-86.
162. Rodrigo C, McKeever TM, Woodhead M, Welham S, Lim WS, British Thoracic S. Admission via the emergency department in relation to mortality of adults hospitalised with community-acquired pneumonia: an analysis of the British Thoracic Society national community-acquired pneumonia audit. Emergency medicine journal : EMJ. 2015;32(1):55-9.
163. England N. NHS Urgent and Emergency Care 2019 [Available from: https://www.nhs.uk/using-the-nhs/nhs-services/urgent-and-emergency-care/nhs-out-of-hours-services/.
164. Textor J, Hardt J, Knuppel S. DAGitty: a graphical tool for analyzing causal diagrams. Epidemiology (Cambridge, Mass). 2011;22(5):745.

165. Uematsu H, Kunisawa S, Yamashita K, Fushimi K, Imanaka Y. Impact of weekend admission on in-hospital mortality in severe community-acquired pneumonia patients in Japan. Respirology (Carlton, Vic). 2016;21(5):905-10.
166. Baldwin HJ, Marashi-Pour S, Chen HY, Kaldor J, Sutherland K, Levesque JF. Is the weekend effect really ubiquitous? A retrospective clinical cohort analysis of 30-day mortality by day of week and time of day using linked population data from New South Wales, Australia. BMJ open. 2018;8(4):e016943.
167. Roberts SE, Thorne K, Akbari A, Samuel DG, Williams JG. Weekend emergency admissions and mortality in England and Wales. Lancet. 2015;385(9980):1829.
168. Daniel P, Rodrigo C, McKeever TM, Woodhead M, Welham S, Lim WS, et al. Time to first antibiotic and mortality in adults hospitalised with community-acquired pneumonia: a matched-propensity analysis. Thorax. 2016;71(6):568-70.
169. Meacock R, Anselmi L, Kristensen SR, Doran T, Sutton M. Higher mortality rates amongst emergency patients admitted to hospital at weekends reflect a lower probability of admission. J Health Serv Res Policy. 2017;22(1):12-9.
170. Chen YF, Armoiry X, Higenbottam C, Cowley N, Basra R, Watson SI, et al. Magnitude and modifiers of the weekend effect in hospital admissions: a systematic review and meta-analysis. BMJ open. 2019;9(6):e025764.
171. Amaral AC, Fowler RA, Pinto R, Rubenfeld GD, Ellis P, Bookatz B, et al. Patient and Organizational Factors Associated With Delays in Antimicrobial Therapy for Septic Shock. Critical care medicine. 2016;44(12):2145-53.
172. Said MA, Johnson HL, Nonyane BA, Deloria-Knoll M, O'Brien KL, Andreo F, et al. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. PloS one. 2013;8(4):e60273.
173. Kandasamy R, Voysey M, Collins S, Berbers G, Robinson H, Noel I, et al. Persistent Circulation of Vaccine Serotypes and Serotype Replacement After 5 Years of Infant Immunization With 13-Valent Pneumococcal Conjugate Vaccine in the United Kingdom. The Journal of infectious diseases. 2019.
174. Ladhani SN, Collins S, Djennad A, Sheppard CL, Borrow R, Fry NK, et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000-17: a prospective national observational cohort study. The Lancet Infectious diseases. 2018;18(4):441-51.
175. Pick H, Daniel P, Rodrigo C, Bewick T, Ashton D, Lawrence H, et al. Pneumococcal serotype trends, surveillance and risk factors in UK adult pneumonia, 2013-18. Thorax. 2019.
176. Djennad A, Ramsay ME, Pebody R, Fry NK, Sheppard C, Ladhani SN, et al. Effectiveness of 23-Valent Polysaccharide Pneumococcal Vaccine and Changes in Invasive Pneumococcal Disease Incidence from 2000 to 2017 in Those Aged 65 and Over in England and Wales. EClinicalMedicine. 2018;6:42-50.
177. Huss A, Scott P, Stuck AE, Trotter C, Egger M. Efficacy of pneumococcal vaccination in adults: a meta-analysis. Cmaj. 2009;180(1):48-58.
178. Thorrington D, Andrews N, Stowe J, Miller E, van Hoek AJ. Elucidating the impact of the pneumococcal conjugate vaccine programme on pneumonia, sepsis and otitis media hospital admissions in England using a composite control. BMC medicine. 2018;16(1):13.
179. Rodrigo C, Bewick T, Sheppard C, Greenwood S, McKeever TM, Trotter CL, et al. Impact of infant 13-valent pneumococcal conjugate vaccine on serotypes in adult pneumonia. The European respiratory journal. 2015;45(6):1632-41.
180. Boddington NL, Warburton F, Zhao H, Andrews N, Ellis J, Donati M, et al. Influenza vaccine effectiveness against hospitalisation due to laboratory-confirmed influenza in children in England in the 2015-2016 influenza season - a test-negative case-control study. Epidemiology and infection. 2019;147:e201-e.
181. Suzuki M, Dhoubhadel BG, Ishifuji T, Yasunami M, Yaegashi M, Asoh N, et al. Serotype-specific effectiveness of 23-valent pneumococcal polysaccharide vaccine against pneumococcal pneumonia in adults aged 65 years or older: a multicentre,

prospective, test-negative design study. The Lancet Infectious diseases. 2017;17(3):313-21.
182. Eletu SD, Sheppard CL, Thomas E, Smith K, Daniel P, Litt DJ, et al. Development of an Extended-Specificity Multiplex Immunoassay for Detection of Streptococcus pneumoniae Serotype-Specific Antigen in Urine by Use of Human Monoclonal Antibodies. Clinical and vaccine immunology : CVI. 2017;24(12).
183. Eletu SD, Sheppard CL, Rose S, Smith K, Andrews N, Lim WS, et al. Re-validation and update of an extended-specificity multiplex assay for detection of Streptococcus pneumoniae capsular serotype/serogroup-specific antigen and cell-wall polysaccharide in urine specimens. Access Microbiology. 2020.
184. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American journal of clinical oncology. 1982;5(6):649-55.
185. Sintes X, Nebot M, Izquierdo C, Ruiz L, DomÍNguez A, Bayas JM, et al. Factors associated with pneumococcal and influenza vaccination in hospitalized people aged ⩾65 years. Epidemiology and infection. 2011;139(5):666-73.
186. StataCorp. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC. 2019.
187. Kim JH, Chun BC, Song JY, Kim HY, Bae IG, Kim DM, et al. Direct effectiveness of pneumococcal polysaccharide vaccine against invasive pneumococcal disease and non-bacteremic pneumococcal pneumonia in elderly population in the era of pneumococcal conjugate vaccine: A case-control study. Vaccine. 2019;37(21):2797-804.
188. Haessler S, Lindenauer PK, Zilberberg MD, Imrey PB, Yu PC, Higgins T, et al. Blood cultures versus respiratory cultures: Two different views of pneumonia. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2019.
189. McLaughlin JM, Jiang Q, Gessner BD, Swerdlow DL, Sings HL, Isturiz RE, et al. Pneumococcal conjugate vaccine against serotype 3 pneumococcal pneumonia in adults: A systematic review and pooled analysis. Vaccine. 2019;37(43):6310-6.
190. Vadlamudi NK, Parhar K, Altre Malana KL, Kang A, Marra F. Immunogenicity and safety of the 13-valent pneumococcal conjugate vaccine compared to 23-valent pneumococcal polysaccharide in immunocompetent adults: A systematic review and meta-analysis. Vaccine. 2019;37(8):1021-9.
191. Sankilampi U, Honkanen PO, Bloigu A, Leinonen M. Persistence of antibodies to pneumococcal capsular polysaccharide vaccine in the elderly. The Journal of infectious diseases. 1997;176(4):1100-4.
192. Vaccines against influenza WHO position paper - November 2012. Releve epidemiologique hebdomadaire. 2012;87(47):461-76.
193. Sherwin RL, Gray S, Alexander R, McGovern PC, Graepel J, Pride MW, et al. Distribution of 13-valent pneumococcal conjugate vaccine Streptococcus pneumoniae serotypes in US adults aged >=50 years with community-acquired pneumonia. Journal of Infectious Diseases. 2013;208(11):1813-20.
194. Isturiz RE, Ramirez J, Self WH, Grijalva CG, Counselman FL, Volturo G, et al. Pneumococcal epidemiology among us adults hospitalized for community-acquired pneumonia. Vaccine. 2019;37(25):3352-61.
195. Hausdorff WP, Feikin DR, Klugman KP. Epidemiological differences among pneumococcal serotypes. The Lancet Infectious diseases. 2005;5(2):83-93.
196. Romney MG, Hull MW, Gustafson R, Sandhu J, Champagne S, Wong T, et al. Large community outbreak of Streptococcus pneumoniae serotype 5 invasive infection in an impoverished, urban population. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2008;47(6):768-74.
197. Pimenta F, Gertz RE, Jr., Park SH, Kim E, Moura I, Milucky J, et al. Streptococcus infantis, Streptococcus mitis, and Streptococcus oralis Strains With Highly Similar cps5 Loci and Antigenic Relatedness to Serotype 5 Pneumococci. Frontiers in microbiology. 2018;9:3199.

198. Public Health England P. Influenza vaccine effectiveness: seasonal estimates 2018 [Available from: https://www.gov.uk/government/publications/influenza-vaccine-effectiveness-seasonal-estimates.
199. Hall VJ, Foulkes S, Saei A, Andrews N, Oguti B, Charlett A, et al. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study. Lancet. 2021;397(10286):1725-35.
200. Feikin DR, Higdon MM, Abu-Raddad LJ, Andrews N, Araos R, Goldberg Y, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. Lancet. 2022;399(10328):924-44.
201. Jackson ML. Use of self-reported vaccination status can bias vaccine effectiveness estimates from test-negative studies. Vaccine: X. 2019;1:100003.
202. Ciabattini A, Nardini C, Santoro F, Garagnani P, Franceschi C, Medaglini D. Vaccination in the elderly: The challenge of immune changes with aging. Seminars in Immunology. 2018;40:83-94.
203. Daniel P, Rodrigo C, Bewick T, Sheppard C, Greenwood S, McKeever TM, et al. Increased incidence of adult pneumococcal pneumonia during school holiday periods. ERJ open research. 2017;3(1).
204. Rodrigo C, Bewick T, Sheppard C, Greenwood S, Macgregor V, Trotter C, et al. Pneumococcal serotypes in adult non-invasive and invasive pneumonia in relation to child contact and child vaccination status. Thorax. 2014;69(2):168-73.
205. Baskaran V, Pearce F, Harwood RH, McKeever TM, Lim WS. Primary care consultations after hospitalisation for pneumonia: a large population-based cohort study. British Journal of General Practice. 2021;71(705):e250-e7.
206. Baskaran V, Murray RL, Hunter A, Lim WS, McKeever TM. Effect of tobacco smoking on the risk of developing community acquired pneumonia: A systematic review and meta-analysis. PloS one. 2019;14(7):e0220204-e.
207. Agusti A, Fabbri LM, Singh D, Vestbo J, Celli B, Franssen FME, et al. Inhaled corticosteroids in COPD: friend or foe? The European respiratory journal. 2018;52(6).
208. Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. Thorax. 2013;68(11):1029-36.
209. Mangera Z DN. National Smoking Cessation Audit Report 2019. British Thoracic Society; 2019.
210. National Institute for Health and Care Excellence N. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. 2019. Contract No.: NG115.
211. 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. The European respiratory journal. 2019;53(3).
212. Ashton D, Pick H, Bains M, Lim W. P24 Patient experience of recovering from pneumonia – a qualitative longitudinal interview study. Thorax. 2018;73(Suppl 4):A109-A.
213. National Institute for Health and Care Excellence: Clinical Guidelines. COVID-19 rapid guideline: managing the long-term effects of COVID-19. London: National Institute for Health and Care Excellence (UK)

214. Song WJ, Hui CKM, Hull JH, Birring SS, McGarvey L, Mazzone SB, et al. Confronting COVID-19-associated cough and the post-COVID syndrome: role of viral neurotropism, neuroinflammation, and neuroimmune responses. Lancet Respir Med. 2021;9(5):533-44.
215. Evans RA, McAuley H, Harrison EM, Shikotra A, Singapuri A, Sereno M, et al. Physical, cognitive and mental health impacts of COVID-19 following hospitalisation – a multi-centre prospective cohort study. medRxiv. 2021:2021.03.22.21254057.
216. Jones BE, Jones J, Bewick T, Lim WS, Aronsky D, Brown SM, et al. CURB-65 pneumonia severity assessment adapted for electronic decision support. Chest. 2011;140(1):156-63.

217. Royal College Physicians R. National Asthma and COPD Audit Programme 2021 [Available from: https://www.nacap.org.uk/.
218. Intensive Care National Audit and Research Centre I. Online reports 2020 [Available from: https://onlinereports.icnarc.org/Home.
219. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. New England Journal of Medicine. 2021;384(16):1491-502.
220. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in Hospitalized Patients with Covid-19. The New England journal of medicine. 2021;384(8):693-704.
221. Normand ST. The RECOVERY Platform. The New England journal of medicine. 2021;384(8):757-8.
222. National Institute for Health and Care Excellence: Clinical Guidelines. COVID-19 rapid guideline: antibiotics for pneumonia in adults in hospital. London: National Institute for Health and Care Excellence (UK)

Copyright © NICE 2020.; 2020.
223. National Institute for Health and Care Excellence: Clinical Guidelines. COVID-19 rapid guideline: critical care in adults. London: National Institute for Health and Care Excellence (UK)

Copyright © NICE 2021.; 2021.
224. Torjesen I. Covid-19: When to start invasive ventilation is “the million dollar question”. BMJ (Clinical research ed). 2021;372:n121.
225. Azoulay E, de Waele J, Ferrer R, Staudinger T, Borkowska M, Povoa P, et al. International variation in the management of severe COVID-19 patients. Critical care (London, England). 2020;24(1):486.
226. Thornton J. The “virtual wards” supporting patients with covid-19 in the community. BMJ (Clinical research ed). 2020;369:m2119.
227. Getting it right first time G. Clinical practice guide for improving the management of adult COVID-19 patients in secondary care. 2020.
228. Organization WH. Position paper on 23-valent pneumococcal polysaccharide vaccine. World Health Organisation; 2008 Octboer 2008.
229. Robert Koch Institut S. Recommentations of the Standing Committee on Vacciantion (STIKO) at the Robert Koch Institue - 2017/2018. 2017:Page 371.
230. Thorrington D, van Rossum L, Knol M, de Melker H, Rumke H, Hak E, et al. Impact and cost-effectiveness of different vaccination strategies to reduce the burden of pneumococcal disease among elderly in the Netherlands. PloS one. 2018;13(2):e0192640.
231. Musher DM, Manoff SB, McFetridge RD, Liss CL, Marchese RD, Raab J, et al. Antibody persistence ten years after first and second doses of 23-valent pneumococcal polysaccharide vaccine, and immunogenicity and safety of second and third doses in older adults. Human Vaccines. 2011;7(9):919-28.
232. Remschmidt C, Harder T, Wichmann O, Bogdan C, Falkenhorst G. Effectiveness, immunogenicity and safety of 23-valent pneumococcal polysaccharide vaccine revaccinations in the elderly: a systematic review. BMC infectious diseases. 2016;16(1):711.
233. Hammitt LL, Bulkow LR, Singleton RJ, Nuorti JP, Hummel KB, Miernyk KM, et al. Repeat revaccination with 23-valent pneumococcal polysaccharide vaccine among adults aged 55-74 years living in Alaska: no evidence of hyporesponsiveness. Vaccine. 2011;29(12):2287-95.
234. Kawakami K, Kishino H, Kanazu S, Takahashi K, Iino T, Sawata M, et al. Time interval of revaccination with 23-valent pneumococcal polysaccharide vaccine more than 5 years does not affect the immunogenicity and safety in the Japanese elderly. Hum Vaccin Immunother. 2018;14(8):1931-8.

235. Kawakami K, Kishino H, Kanazu S, Toshimizu N, Takahashi K, Sterling T, et al. Revaccination with 23-valent pneumococcal polysaccharide vaccine in the Japanese elderly is well tolerated and elicits immune responses. Vaccine. 2016;34(33):3875-81.
236. Musher DM, Manoff SB, Liss C, McFetridge RD, Marchese RD, Bushnell B, et al. Safety and Antibody Response, Including Antibody Persistence for 5 Years, after Primary Vaccination or Revaccination with Pneumococcal Polysaccharide Vaccine in Middle-Aged and Older Adults. The Journal of infectious diseases. 2010;201(4):516-24.
237. Törling J, Hedlund J, Konradsen HB, Ortqvist A. Revaccination with the 23-valent pneumococcal polysaccharide vaccine in middle-aged and elderly persons previously treated for pneumonia. Vaccine. 2003;22(1):96-103.
238. Nakamura A, Kawakami K, Wakana A, Folaranmi TA, Iino T. A Japanese nationwide survey of 23-valent pneumococcal capsular polysaccharide vaccine (PPSV23) revaccination coverage rate among elderly adults aged 65 and older and physician's attitude. Hum Vaccin Immunother. 2020;16(9):2292-9.
239. Caya CA, Boikos C, Desai S, Quach C. Dosing regimen of the 23-valent pneumococcal vaccination: a systematic review. Vaccine. 2015;33(11):1302-12.
240. Takashima M, Lambert SB, Paynter S, Ware RS. Relative effectiveness of revaccination with 23-valent pneumococcal polysaccharide vaccine in preventing invasive pneumococcal disease in adult Aboriginal and Torres Strait Islander people, Australia. Vaccine. 2019;37(12):1638-41.
241. Hurley D, Griffin C, Young M, Scott DA, Pride MW, Scully IL, et al. Safety, Tolerability, and Immunogenicity of a 20-Valent Pneumococcal Conjugate Vaccine (PCV20) in Adults 60 to 64 Years of Age. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2020.
242. Thompson A, Lamberth E, Severs J, Scully I, Tarabar S, Ginis J, et al. Phase 1 trial of a 20-valent pneumococcal conjugate vaccine in healthy adults. Vaccine. 2019;37(42):6201-7.

Chapter 10 Appendix

10.1 Search terms used for Ovid Medline:

1. exp PNEUMONIA/ or pneumonia.mp.
2. exp Respiratory Tract Infections/
3. lower respiratory tract infection.mp.
4. community acquired infection.mp. or exp Community-Acquired Infections/
5. exp "OUTCOME AND PROCESS ASSESSMENT (HEALTH CARE)"/
6. exp MORTALITY/ or mortality.mp.
7. exp Hospitalization/
8. exp "Quality of Health Care"/
9. exp spatial analysis/
10. exp GEOGRAPHY, MEDICAL/
11. geographic varia*.mp.
12. 1 or 2 or 3
13. 4 and 12
14. 5 or 6 or 7 or 8
15. exp "Length of Stay"/
16. 14 or 15
17. 13 and 16
18. limit 17 to "all adult (19 plus years)"

19. exp RESPIRATORY TRACT DISEASES/

20. 9 or 10 or 11

21. 19 and 20

22. limit 21 to "all adult (19 plus years)"

23. 18 or 22

24. 17 or 21

10.2 Newcastle-Ottawa Quality Assessment Form for Cohort Studies – Modified

Modified Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Note: A study can be given a maximum of one point for each numbered item within the Selection and Outcome categories. A maximum of two points can be given for Comparability.

Selection

1) Are the subunits compared (eg hospital, region) representative?

a) Truly representative (one point)

b) Somewhat representative (one point)

c) Selected group

d) No description of the derivation of the cohort

2) Are the patient populations within the hospitals/regions representative and comparable?

a) Truly comparable (one point)

b) Somewhat comparable (one point)

c) Selected group

d) No description of the derivation of the cohort

3) Ascertainment of process of care measures:

a) Medical record notes review by an independent assessor (one point)

b) Recorded from recognised database (one point)

c) Self report

d) No description

e) Other

4) Adequacy of process of care measure data recorded:

a) Complete data - all subject accounted for (one point)

b) Subjects without process of care data unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. (one point)

c) Follow up rate less than 80% and no description of those lost

d) No statement

5) Are any missing process of care measure or outcome data points accounted for?

a) The authors make a statement addressing reasons for missing outcome and process of care data (one point)

b) The authors do not make a statement accounting for missing data points.

Comparability

1) Has the study compared hospital/regional characteristics and adjusted for differences in statistical analysis?:

a) The study analyses and controls for hospital/regional characteristics in its analysis (one point)

b) The study analyses hospital/regional characteristics but does not control for them (half point)

c) Hospital characteristics not compared or adjusted for

2) Has the study compared patient cohort characteristics at each hospital/region and adjusted for differences in statistical analysis?:

a) The study controls for age and severity of illness in the populations in each area (one point)

b) Study controls for the above and other factors (one point)

If so, which factors:

c) No attempt recorded to compare cohort characteristics or adjust accordingly.

Outcome

1) Assessment & recording of outcome measures:

a) Patient or proxy interview (one point)

b) Medical record review or linkage (one point)

c) Self report

d) No description

e) Other

3) Adequacy of outcome data recorded:

a) Complete outcome data - all subject accounted for (one point)

b) Subjects without outcome data unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. (one point)

c) Follow up rate less than 80% and no description of those lost

d) No statement

3) Were the authors transparent regarding affiliations and financial incentives?

a) Yes both (one point)

b) Yes – one only (half point)

c) No comment on either

SCORE:

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: 3 or 4 points in selection domain AND 1 or 2 points in comparability domain AND 2 or 3 points in outcome/exposure domain

Fair quality: 2 points in selection domain AND 1 or 2 points in comparability domain AND 2 or 3 points in outcome/exposure domain

Poor quality: 0 or 1 points in selection domain OR 0 points in comparability domain OR 0 or 1 points in outcome/exposure domain