MORBIDITY OF COMMUNITY-ACQUIRED PNEUMONIA

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Table of Contents

Abstract _____ **vii**

Publications _____ **x**

Awards _____ **xii**

Presentations _____ **xiii**

Acknowledgements _____ **xv**

List of figures _____ **xvii**

List of tables _____ **xx**

Abbreviations _____ **xxiii**

Chapter 1 Introduction _____ **1**

1.1 Definition of pneumonia 2
1.2 Incidence 3
1.3 Economic burden 4
1.4 Aetiology 5
1.5 Risk factors 6
1.6 Mortality 7
1.7 Morbidity 9
1.8 Thesis objectives 10
1.9 Outline of chapters 12

Chapter 2 Methods for studies using Clinical Practice Research Datalink (CPRD), linked to Hospital Episode Statistics (HES) _____ **15**

2.1 Ethical approval 16
2.2 Data sources 16
2.2.1 Primary care data 16
2.2.2 Data linkage 18
2.2.3 Generalisability and validity of data 20
2.3 Study population 22
2.4 Building the dataset: Definition of key variables 22
2.4.1 Definition of pneumonia 22
2.4.2 Definition of covariates in CPRD 23

Chapter 3 Primary care consultations following hospitalisation for pneumonia __ **26**

3.1 Introduction 27
3.2 Methods 28
3.2.1 Study population and follow-up 28
3.2.2 Definitions 28
3.2.3 Patient involvement 29
3.2.4 Statistical analysis 29
3.3 Results 32
3.3.1 Factors associated with consultation 35
3.3.2 Reasons for consultations and readmissions 42
3.3.3 Antibiotic prescription at consultation 44
3.4 Discussion 47
3.4.1 Principal findings 47
3.4.2 Strengths & Weakness of the study 47
3.4.3 Comparison with other studies 48
3.4.4 Possible explanations & implications for clinicians & policymakers 50
Chapter 4 Cardiac complications following community-acquired pneumonia: A systematic review and meta-analysis _____ 53
4.1 Introduction 54
4.2 Methods 55
4.2.1 Search strategy and study selection 55
4.2.2 Data extraction and assessment of methodological quality 56
4.2.3 Data synthesis & Statistical analysis 57
4.3 Results 58
4.3.1 Characteristics on included studies 59
4.3.2 Risk of bias 72
4.3.3 Incidence of cardiac complications after CAP 74
4.3.4 Risk factors for developing cardiac complications 83
4.3.5 Mortality associated with cardiac complications 88
4.3.6 Biomarkers 90
4.4 Discussion 91
4.4.1 Principal findings 91
4.4.2 Strengths and limitations of the study 91
4.4.3 Comparison with other studies 92
4.4.4 Cardiac complications after CAP: mechanisms 94
4.4.5 Implications for clinicians and policymakers 95
4.4.6 Conclusion 97

Chapter 5 Matched cohort study of cardiac complications in adults hospitalised with pneumonia _____ 98

5.1 Introduction 99
5.2 Methods 99
5.2.1 Data sources 99
5.2.2 Study population and follow-up 99
5.2.3 Definition of outcome 100
5.2.4 Statistical analysis 100
5.3 Results 103
5.4 Discussion 117
5.4.1 Principal findings 117
5.4.2 Strengths and limitations of the study 117
5.4.3 Comparison with other studies 118
5.4.4 Implications for clinicians and policymakers 120
5.5 Conclusion 121

Chapter 6 Effect of tobacco smoking on the risk of developing community acquired pneumonia: A systematic review and meta-analysis _____ 122

6.1 Introduction 123
6.2 Methods 124
6.2.1 Search strategy and study selection 124
6.2.2 Data extraction and assessment of methodological quality 125
6.2.3 Data synthesis 126
6.3 Results 127
6.3.1 Characteristics of included studies 128
6.3.2 Risk of bias 144
6.3.3 Smoking status 145
6.3.4 Meta-analyses 146
6.3.5 Dose-response trend: narrative review 152
6.4 Discussion 153
6.4.1 Tobacco smoking and infection: immune mechanisms 155
6.4.2 Effect of tobacco smoking cessation 155
6.4.3 Strengths and limitations 156
6.4.4 Implications 157

Chapter 7 Tobacco smoking is an important modifiable risk factor for recurrent hospitalisation with pneumonia _____ 159

7.1 Introduction 160

7.2 Methods 160
7.2.1 Study population and follow-up 160
7.2.2 Definitions 162
7.2.3 Statistical analysis 162
7.3 Results 164
7.4 Discussion 169
7.4.1 Principal findings 169
7.4.2 Comparison with other studies 169
7.4.3 Strengths and weaknesses of the study 171
7.4.4 Implications 172
7.4.5 Conclusion 173
Chapter 8 Co-infection in COVID-19: A retrospective multicentre study in patients admitted to the Intensive Care Unit 175
8.1 Introduction 176
8.2 Methods 177
8.2.1 Data source 177
8.2.2 Study population 177
8.2.3 Data collection 178
8.2.4 Definitions 179
8.2.5 Statistical analysis 180
8.3 Results 182
8.4 Discussion 191
8.4.1 Principal findings 191
8.4.2 Comparison with literature: 191
8.4.3 Strengths and limitations 193
8.4.4 Implications for future work 194
Chapter 9 Conclusion 196
9.1 Key findings 197
9.2 Implications 198
9.3 Future research recommendations 200
9.4 Conclusion 204
References 206
Appendix 249
Appendix 1: ISAC Protocol 250
Appendix 2: Read codes 294
Comorbidities 294

Smoking status 375
Alcohol status 377
Appendix 3: PROSPERO Registration (Chapter 4) 379
Appendix 4: SR Search terms (Chapter 4) 389
Appendix 5: Data extraction form (Chapter 4) 391
Appendix 6: Codes for Chapter 5 398
Appendix 7: PROSPERO Registration (Chapter 6) 403
Appendix 8: SR Search terms (Chapter 6) 408
MEDLINE (Ovid) 408
Embase (Ovid) 409
PsycINFO (Ovid) 410
Web of Science 411
Appendix 9: Data extraction form (Chapter 6) 412
Appendix 10: Read codes for Chapter 7 418
Stop smoking interventions 418
Appendix 11: Results and classification as likely pathogen or contaminant among positive cultures taken from patients (Chapter 8) 423

Abstract

Background

Community acquired pneumonia (CAP) accounts for 5-12% of lower respiratory tract infections presenting to primary care in the UK. Of patients who present to their GP with suspected CAP, 22- 42% are referred to hospital for further management in the UK. The majority of patients (~90%) admitted for CAP survive to hospital discharge. However, little is known about the morbidity related to recovery from pneumonia.

Methods

Three studies in this thesis used large-scale hospitalisation data from Hospital Episode Statistics (HES, England), linked to the Clinical Practice Research Datalink (CPRD), and death registration data from Office for National Statistics (ONS). These studies aim to improve our understanding on the morbidity after CAP and the objectives were:

(1) to describe the primary care consultations after pneumonia and the reasons for these consultations
(2) to determine the incidence of, and risk factors for developing cardiac complications
(3) to determine the incidence of recurrent hospitalisation for pneumonia and the association of tobacco smoking.

In addition, published literature on cardiac complications, a major morbidity following CAP and tobacco smoking and passive smoke exposure as a risk factor for developing CAP were systematically summarised.

Finally, a multicentre retrospective study was conducted during the first wave of COVID-19 pandemic to determine the proportion of laboratory proven co-infection in critically ill adults with COVID-19 infection in England.

Results

This thesis found a previously unrecognised large burden of morbidity during recovery from pneumonia; 56% of patients consulted primary care within 30 days of discharge. The highest rate of consultation occurred early, within the first 7 days (4.7 per 100 person-days). Nearly 40% of consultations were for a respiratory disorder and 30% of patients consulting received further antibiotics within 30 days of discharge.

The systematic review (n=47 studies) found in-hospital incidence of cardiac complications of between 3-8%. Patients who developed cardiac complications were more likely to die both in-hospital (odds ratio (OR) 3.45, 95% CI 2.38-4.99) and within 30 days (OR 2.65, 95% CI 1.24-5.68) of admission than those who did not. Data from the population-based study showed that those with pneumonia were significantly at higher risk of developing all cardiac complications compared to those without pneumonia. The highest risk was observed for developing arrhythmia at 30 days after discharge (subhazard ratio (sHR) 9.51, 95% CI 8.35-10.83).

The systematic review (n=27 studies) found that current and ex-smokers were both significantly at higher risk of developing CAP whilst passive tobacco smoke exposure had a significant effect only in those aged ≥ 65. A dose-response trend with higher risk of CAP amongst current smokers who smoke higher amounts of tobacco was noted. From the population-based study, 9% of patients hospitalised with index pneumonia developed recurrent pneumonia within a year of follow-up. Current tobacco smoking status at index

hospitalisation for pneumonia was independently associated with a higher risk of recurrent pneumonia.

Finally, bacterial co-infection within 48 hours of hospital admission for COVID-19 infection in adults was uncommon; 1.6% on admission and 5.5% within 48 hours. Patients with co-infections were more likely to die in ICU (crude OR 1.78, 95% CI 1.03-3.08) compared to those without co-infections.

Conclusion

In conclusion, this thesis highlights that patients experience a significant morbidity during recovery from pneumonia. A better understanding of the morbidity after CAP is necessary to develop and implement appropriate interventions to improve the long-term outcomes of patients hospitalised with CAP.

Publications

Original research publications arising from this thesis

Baskaran V, Pearce F, Harwood F, McKeever T, Lim WS. Primary Care Consultations after Hospitalisation for Pneumonia: A Large Population-based Cohort Study. British Journal of General Practice. 2020 Dec 14. DOI: https://doi.org/10.3399/BJGP.2020.0890

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. doi:10.1371/journal.pone.0220204

Baskaran V, Lim WS, McKeever T. Tobacco smoking is an important modifiable risk factor for recurrent hospitalisation with pneumonia: A population-based cohort study. Thorax 2021 Jun 18. doi: 10.1136/thoraxjnl-2020-216494

Baskaran V, Lawrence H, Lansbury L et al. Co-infection in critically ill patients with COVID-19: An observational cohort study from England. J Med Microbiol. 2021 Apr 16; 70(4):001350.

Other original research publications related to this thesis

Lawrence H, Pick H, **Baskaran V,** Daniel P, Rodrigo C, Ashton D, Edwards-Pritchard RC, Sheppard C, Eletu SD, Litt D, Fry NK. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against vaccine serotype pneumococcal pneumonia in adults: A case-control test-negative design study. PLoS medicine. 2020 Oct 23;17(10):e1003326.

Lansbury L, Lim B, **Baskaran V**, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. Journal of Infection. 2020 May 27.

Pick H, Daniel P, Rodrigo C, Bewick T, Ashton D, Lawrence H, **Baskaran V,** Edwards-Pritchard RC, Sheppard C, Eletu SD, Rose S. Pneumococcal serotype trends, surveillance and risk factors in UK adult pneumonia, 2013–18. Thorax. 2020 Jan 1;75(1):38-49.

Baskaran V (contributor), Tobacco Advisory Group of the Royal College of Physicians. (June 2018). Hiding in plain sight: Treating tobacco dependency in the NHS.

Articles unrelated to the thesis

WS Cho, Q Bonduelle, A Ghasemi, **V Baskaran,** R O'Connor, J Shah, F Andrewartha, N Fergie. Prognosticating patients with necrotising otitis externa based on response to treatment. Ann R Coll Surg Engl 2021; 000: 1–6. doi 10.1308/rcsann.2020.7133

Bolaji OM, Zainudin NI, Snape S, Saini G, **Baskaran V.** Images of the month: The conundrum of chronic coccidioidomycosis. Clinical Medicine. 2021 Jan 1;21(1):e110-1.

Awards

- Shortlisted for the Respiratory Specialist Registrar Award, organised by The Royal Society of Medicine

- British Lung Foundation (BLF) Virtual Travel Fellowship Award to support the attendance of the 2020 European Respiratory Society Annual Conference and presentation of two posters (August 2020):
  i. "Meta-analysis of Acute Coronary Syndrome in Patients with Community-Acquired Pneumonia"
  ii. "Incidence of Cardiac Complications after Hospitalisation for Community Acquired Pneumonia: A Large Population-based Cohort Study"

- Three-Minute Thesis (3MT) Competition: Second runner-up for Judges' Award & People's Choice Award (June 2020)

- Sue Watson Postgraduate Oral Presentation Event (March 2020)- First Prize

- Travel Bursary from Divisional Development Fund (Epidemiology and Public Health Division) to support the attendance of European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) and poster presentation (February 2020): "Primary Care Re-consultation after Hospitalisation for Community Acquired Pneumonia in England: A Large Population-based Cohort Study"

- Best Oral Presentation at East Midlands Thoracic Society (EMTS) Conference (Nov 2019)

Presentations

International

- Poster Discussion presentation: Meta-analysis of Acute Coronary Syndrome in Patients with Community-Acquired Pneumonia/ European Respiratory Society Congress (Virtual) (Sept 2020)

- Poster Discussion presentation: Incidence of Cardiac Complications after Hospitalisation for Community Acquired Pneumonia: A Large Population-based Cohort Study/ European Respiratory Society Congress (Virtual) (Sept 2020)

- Oral presentation: Meta-analysis of the Effect of Current Tobacco Smoking on the Risk of Developing Community Acquired Pneumonia/ GSK SpR Symposium, Paris (Sept 2018)

- Poster Discussion presentation: Meta-analysis of the Effect of Current Tobacco Smoking on the Risk of Developing Community Acquired Pneumonia/ European Respiratory Society Congress, Paris (Sept 2018)

National

- Oral presentation: Burden on Primary care after hospitalisation for pneumonia: A large population-based cohort study/ The Royal Society of Medicine: Respiratory student and trainee prize meeting (Jan 2020)

- Oral presentation: Primary care reconsultation after community-acquired pneumonia: a large population-based cohort study/ British Thoracic Society Winter Meeting (Dec 2019)

Regional

- Oral presentation: Primary care re-consultation after community-acquired pneumonia: a large population-based cohort study/ East Midlands Thoracic Society Conference (Nov 2019)

- Poster presentation: Meta-analysis of the Effect of Current Tobacco Smoking on the Risk of Developing Community Acquired Pneumonia/ East Midlands Thoracic Society Conference (Oct 2018)

Local

- Oral presentation: Burden on primary care following hospitalisation for pneumonia/ Three-Minute Thesis Competition, University of Nottingham (June 2020)

- Oral presentation: Primary care reconsultation after community-acquired pneumonia: a large population-based cohort study/ Sue Watson Postgraduate Oral Presentation Event, University of Nottingham (March 2020)

- Oral presentation: Meta-analysis of the Effect of Tobacco Smoking on the Risk of Developing Community Acquired Pneumonia/ Doctor in Training Conference, Nottingham University Hospitals NHS Trust (July 2019)

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List of figures

Fig 3-1: Flowchart of the study population 32
Fig 3-2: Kaplan- Meier plot of time to first consultation 34
Fig 3-3: Trend of primary care consultation over the 15-year study period 35
Fig 3-4: Trend of antibiotics prescription at primary care consultation over the 15-year study period 45
Fig 4-1: PRISMA flow diagram for study selection 58
Fig 4-2: Forest plot of proportions of in-hospital overall cardiac complications after community-acquired pneumonia 76
Fig 4-3: Forest plot of proportions of ACS on admission after community-acquired pneumonia 76
Fig 4-4: Forest plot of proportions of ACS in-hospital after community-acquired pneumonia 77
Fig 4-5: Forest plot of proportions of ACS at 30 days after community-acquired pneumonia 77
Fig 4-6: Forest plot of proportions of ACS at 90 days after community-acquired pneumonia 78
Fig 4-7: Forest plot of proportions of heart failure on admission after community-acquired pneumonia 78
Fig 4-8: Forest plot of proportions of heart failure in-hospital after community-acquired pneumonia 79
Fig 4-9: Forest plot of proportions of heart failure at 30 days after community-acquired pneumonia 79
Fig 4-10: Forest plot of proportions of heart failure at 90 days after community-acquired pneumonia 80
Fig 4-11: Forest plot of proportions of heart failure at 1 year after community-acquired pneumonia 80
Fig 4-12: Forest plot of proportions of arrhythmia on admission after community-acquired pneumonia 81
Fig 4-13: Forest plot of proportions of arrhythmia in-hospital after community-acquired pneumonia 81
Fig 4-14: Forest plot of proportions of arrhythmia at 30 days after community-acquired

pneumonia 82
Fig 4-15: Forest plot of mortality associated with overall cardiac complications after CAP 88
Fig 4-16: Forest plot of mortality associated with ACS after CAP 89
Fig 5-1: Directed Acyclic Graph illustrating the association between admission for pneumonia (exposure) and developing cardiac complications (outcome). 102
Fig 5-2: Kaplan-Meier plots of incidence of time to first cardiac complication in patients with and without pneumonia. 107
Fig 5-3: Incidence rate for all cardiac complications by year of admission for pneumonia. 108
Fig 6-1: PRISMA flow diagram for study selection 127
Fig 6-2: Meta-analysis of risk of community acquired pneumonia in current smokers relative to never smokers (Odds Ratio). 147
Fig 6-3: Funnel plot for the association between current smoking and the risk of developing CAP 148
Fig 6-4: Meta-analysis of incidence of community acquired pneumonia in current smokers relative to never smokers (Hazards Ratio) 148
Fig 6-5: Meta-analysis of risk of community acquired pneumonia in current smokers relative to 'not current' smokers (Odds Ratio) 149
Fig 6-6: Meta-analysis of risk of community acquired pneumonia in current smokers relative to 'ever' smokers (Odds Ratio) 149
Fig 6-7: Meta-analysis of risk of community acquired pneumonia in ex-smokers relative to never smokers (Odds Ratio) 150
Fig 6-8: Meta-analysis of incidence of community acquired pneumonia in ex-smokers relative to never smokers (Hazards Ratio) 151
Fig 7-1: Directed Acyclic Graph illustrating the association between smoking status (exposure) and developing recurrence of pneumonia (outcome). 163
Fig 7-2: Flowchart of study population 164
Fig 7-3: Nelson-Aalen plot of cumulative incidence of pneumonia recurrence in the first 5 years after index pneumonia 165
Fig 7-4: Trend of recurrence of pneumonia within 30-90 days and 1 year of index pneumonia admission 166
Fig 8-1: Flowchart of study population 182
Fig 8-2: Bacterial pathogens detected after 48 hours of hospital admission; 124 potential

pathogens detected.. 189

List of tables

Table 1-1: Risk factors adapted from systematic review by Almirall et al.[26] 6
Table 2-1: Data files supplied by CPRD and used in this thesis 18
Table 2-2: Data sources linked to CPRD primary care records used in this thesis. 20
Table 2-3: ICD-10 codes for pneumonia 22
Table 3-1: Pattern of missing data for smoking status and alcohol consumption 30
Table 3-2: Characteristics of the overall study population 33
Table 3-3: Univariate and multivariate competing-risks regression analyses investigating the predictors of primary care consultation after hospitalisation for pneumonia in the first 30 days after discharge 36
Table 3-4: Sensitivity analysis excluding primary care consultation in the previous year . 40
Table 3-5: Reasons for GP consultation after hospital discharge 42
Table 3-6: Top 20 reasons for readmission 43
Table 3-7: Antibiotic prescription at consultation 44
Table 3-8: Univariate and multivariate logistic regression analyses investigating the important predictors of antibiotic prescription in patients who consulted within the first week of discharge. 45
Table 4-1: Characteristics of 47 included studies for systematic review; ordered by year. 60
Table 4-2: Risk of bias for included studies (using Newcastle Ottawa Scale) 73
Table 4-3: Incidence of cardiac complications after CAP 75
Table 4-4: Risk factors for developing overall cardiac complications in-hospital, at 30 days and at 1 year 84
Table 4-5: Risk factors of developing individual cardiac complications after CAP 86
Table 4-6: Mortality associated with cardiac complications 89
Table 5-1: Characteristics of patients with and without pneumonia at 30 days, categorised by cardiac complications (ACS, heart failure and arrhythmia) 104
Table 5-2: The proportion of ACS, heart failure and arrhythmia after hospitalisation for pneumonia. 105
Table 5-3: Incidence rates (per 1000 person-years) of ACS, HF and arrhythmia after hospitalisation for pneumonia 105
Table 5-4: Absolute increase in events (per 10,000 patients) in patients with pneumonia

compared to those without pneumonia in the short and long-term. 106
Table 5-5: Competing-risks regression for the risk of developing ACS in patients with and without pneumonia, and the factors associated with the risk of developing ACS. 109
Table 5-6: Competing-risks regression for the risk of developing heart failure in patients with and without pneumonia, and the factors associated with the risk of developing heart failure. 112
Table 5-7: Competing-risks regression for the risk of developing arrhythmia in patients with and without pneumonia, and the factors associated with the risk of developing arrhythmia. 115
Table 6-1: Characteristics of 27 included studies for systematic review; ordered by year, author. 129
Table 6-2: Risk of bias for included studies (using Newcastle Ottawa Scale) 144
Table 6-3: Smoking categories used in included studies 145
Table 6-4: Dose-response relationship between amount of smoking and risk of developing CAP. Trend (OR)* of 1.xy means xy% increase of risk of CAP per increase in category documented in the 'Quantification of smoking exposure' column. 152
Table 7-1: Factors independently associated with recurrent pneumonia within a year of discharge: Competing-risks regression (CRR) analysis with death as competing event ... 167
Table 7-2: Current smokers who were given stop smoking interventions before admission for index pneumonia or after discharge 168
Table 8-1: Definition (based on ICNARC report on COVID-19 in critical care)[308] 178
Table 8-2: Viral testing panel by study site 180
Table 8-3: Study population by study site 183
Table 8-4: Characteristics of study population in comparison with ICNARC data 184
Table 8-5: Organisms identified within 48 hours of hospital admission 186
Table 8-6: Co-infection rate within 48 hours (1000 person-days) for the overall study population and excluding the hospital which contributed a third of cases. 186
Table 8-7: Number of tests performed within 48 hours of hospital admission, by type of tests 187
Table 8-8: Antimicrobial susceptibilities for identified bacterial pathogens 188
Table 8-9: Univariate logistic regression analyses investigating the association between variables of interest and odds of developing co-infection/ co-colonisation. 190
Table 9-1: A future study using PICO framework 201

Abbreviations

ACS	Acute coronary syndrome
aOR	Adjusted odds ratio
APACHE	Acute Physiology and Chronic Health Evaluation
BNF	British National Formulary
BTS	British Thoracic Society
CAP	Community acquired pneumonia
CCI	Charlson Comorbidity Index
CCF	Congestive cardiac failure
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
CVA	Cerebrovascular accident
CXR	Chest X-ray
ED	Emergency Department
GP	General practitioner
HAP	Hospital acquired pneumonia
HES	Hospital Episode Statistics
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
ICD	International Classification of Diseases
LOS	Length of stay
LRTI	Lower respiratory tract infection
MeSH	Medical Subject Headings
MI	Myocardial infarction
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
ONS	Office for National Statistics
OR	Odds ratio
RCT	Randomised controlled trial
sHR	Subhazard ratio
UK	United Kingdom
UTS	Up to standard (date)

Chapter 1

Chapter 1 Introduction

This introductory chapter provides an overview of community acquired pneumonia (CAP), the incidence, economic burden, aetiology, risk factors, as well as associated morbidity and mortality. Detailed objectives of the thesis are summarised at the end of the chapter.

1.1 Definition of pneumonia

Clinical features of CAP include fever (>38°C), cough, dyspnoea, sputum production, pleuritic chest pain, and non-specific features in the elderly such as 'off legs' and confusion, in the absence of fever.[1] Physical examination signs that suggest pneumonia include raised respiratory rate, tachycardia, and new and localizing signs on chest examination such as reduced chest expansion on the affected side, with signs consistent with consolidation (dull percussion note, reduced air entry with bronchial breathing, increased vocal resonance) and crackles. The diagnosis of CAP is unlikely if the chest examination is normal.

The British Thoracic Society (BTS)[2] defined CAP in hospital as:

- symptoms and signs consistent with an acute lower respiratory tract infection associated with new radiographic shadowing for which there is no other explanation (e.g., not pulmonary oedema or infarction), and
- the illness is the primary reason for hospital admission and is managed as pneumonia

Community acquired pneumonia accounts for 5- 12% of non-pneumonic lower respiratory tract infections (LRTIs) presenting to general practitioners (GP).[2,3] As a result, the recognition and diagnosis of suspected CAP in the community may be more challenging as it is based on clinical features alone, without the benefit of the gold

standard chest radiograph. Although there is a high sensitivity (91%-95%), clinical diagnosis without radiographic evidence has a low specificity of 40%-56%.[4,5]

1.2 Incidence

In 2013, Torres et al. summarised the incidence of CAP from 16 studies from the UK, Italy, Spain, France, Germany and Denmark; the overall annual incidence of CAP in adults ranged from 1.07-1.2/1000 person-years and 1.54-1.7/1000 population.[6] Of patients who present to their GP with suspected CAP, 22- 42% are referred to hospital for further management in the UK.[3] Data from Hospital Episode Statistics (HES) Admitted Patient Care activity 2019/2020 reported over 288,000 patients admitted to hospital had a primary diagnosis of pneumonia (ICD-10 J12-J18) and 6% of admissions had pneumonia recorded in any diagnostic field.[7]

The most recent incidence of CAP requiring hospitalization in the UK was 0.80/1000 adults (95% CI 0.77– 0.83) between 2008-2013 using a prospective cohort study design.[8] This incidence was comparable to that reported by a Spanish study with similar design, 0.90/1000 (95% CI 0.77- 1.00).[9] An increasing trend of CAP incidence rate was observed by Quan et al. in their 16-year study using coded data in the UK; 4.2%/ year (95% CI 3.6-4.8) increase from 1998-2008, and subsequently 8.8%/ year (95% CI 7.8-9.7) increase from 2009- 2014.[10] A similar trend was observed in those over 65 years; Millett et al. reported the average predicted probability of hospitalisation for CAP markedly rose by 29% between 1998-2010.[11] Of note, higher incidence rate amongst males and older people, particularly over the age of 65 years have been consistently reported in the literature.

1.3 Economic burden

CAP carries a significant burden of cost to the NHS. The average cost for managing pneumonia in the community was estimated at £100 per episode compared to hospitalisation cost of £1700–5100.[12] In 1992/93, the annual cost was estimated at £441 million, mostly (87%) associated with inpatient care cost.[12] In this analysis, there were 261,000 annual episodes of CAP, with approximately 83,153 annual cases of CAP (32% of all episodes) which required hospital admission. The average length of stay is 7.8 days for patients who are 65 and above, and shorter at 5.8 days for younger patients.[13] Following an episode of hospitalised CAP, adults with underlying comorbidities were found to have subsequent higher healthcare resource utilisation with higher hospital admission costs during a 3-year follow-up period compared to matched controls who did not have an episode of CAP.[14] In addition, sickness absence in general is estimated to cost the UK economy approximately £15 billion annually.[15] With rising incidence and admissions for CAP, it is likely that the economic burden of CAP in the UK will continue to rise.

The economic burden of both direct and indirect costs of CAP globally will need to take into account the type of healthcare system, admission criteria, average length of hospital stay and functional impairment after hospitalisation including return to work, job loss and loss of independence or short-term disability. In the US, the national direct and indirect costs of CAP in the working-age adults was estimated at $8.5 billion and $2.1 billion respectively.[16] The costs of healthcare, sick time and short-term disability increased with advancing age and higher risk status (based on underlying co-morbidities) in working-age adults.[17] The indirect costs resulting from sick time and short-term disability were substantially higher in an employee with CAP compared to an employee without CAP;

mean annual costs of $1129 vs $853 for sick time and $1016 vs $322 for short-term disability.

1.4 Aetiology

Where an aetiology is found, a single pathogen is identified in 85% of patients, though the true frequency of polymicrobial CAP is not known.[2] *Streptococcus pneumoniae* is the commonest pathogen identified globally. Welte et al. extensively analysed the aetiology of CAP in European adults.[18] In addition to *S. pneumoniae*, other bacterial pathogens identified in decreasing frequency were *H. influenzae*, *Legionella* spp, *Chlamydophila* spp, *Mycoplasma pneumoniae*, *Staphylococcus* spp, Gram-negative bacilli, *Moraxella catarrhalis* and *Coxiella burnetti.* For patients managed on the ICU, *Legionella* spp and *S. aureus* were identified more frequently.

Meta-analysis of 31 studies which mostly obtained polymerase chain reaction (PCR) via nasopharyngeal or oropharyngeal swab, found a high proportion of viral infection in patients with CAP; 24.5% (95% CI 21.5-27.5).[19] The proportion was higher in studies which obtained lower respiratory samples; 44.2% (95% CI 35.1-53.3). The most commonly identified viruses were influenza, rhinovirus, respiratory syncytial virus and coronavirus.

Community-acquired pneumonia is a result of the interplay between the host, microbes and environmental factors. Hendley et al. found that adults with preschool children in the family (18%) had higher *Streptococcus pneumoniae* carriage rates than adults without preschool children in the family (2-9%).[20] In a large observational study of 2221 patients, Daniel et al. found adults admitted to hospital with a diagnosis of CAP during school

holiday periods were significantly more likely to report child contact prior to hospital admission (35.3% *vs* 26.7%; aOR 1.38, 95% CI 1.11–1.72, p=0.004) and were significantly more likely to have pneumococcal infection compared to those admitted during term time (42.0% *vs* 33.7%, OR 1.43, 95% CI 1.00–2.03, p=0.046).[21] Various studies have shown that transmission of *S. pneumoniae* occur by close contact with a carrier (especially young children), large-droplet secretions or via fomites and intercurrent viral respiratory tract infection.[22–25]

1.5 Risk factors

A systematic review by Almirall et al. in 2017 identified several risk factors for developing CAP from 29 observational studies.[26] The authors divided the risk factors into three categories, namely 'clear risk factor', 'no effect' and when the evidence was 'inconclusive'.

Table 1-1: Risk factors adapted from systematic review by Almirall et al.[26]

Conclusion from systematic review	Risk factor
Clear risk factor	Sociodemographic and lifestyle Factors • older age • smoking • environmental exposures to different substances (home, occupational and environment) Comorbidities/ clinical conditions • COPD • asthma • malnutrition • previous CAP • functional impairment • poor dental health Medications • immunosuppressive therapy • oral steroids • gastric acid-suppressive drugs
No effect	Sociodemographic and lifestyle Factors

	• raised BMI • passive smoking Comorbidities/ clinical conditions • chronic renal disease Medications • use of antibiotics before CAP • influenza vaccine
Inconclusive	Sociodemographic and lifestyle Factors • male gender • alcohol use • passive smoking in the older age subgroup Comorbidities/ clinical conditions • heart disease • dysphagia • cancer • chronic liver disease • diabetes Medications • inhalers • pneumococcal vaccine

1.6 Mortality

Lower respiratory tract infections (LRTIs), including CAP were reported as the 'most deadly communicable disease' worldwide in 2016, causing 3.0 million deaths.[27] The Global Burden of Disease Study 2019 reported LRTIs were the fourth leading cause of worldwide deaths in 2019 with an age standardised death rate of 34.3/100,000 (95% CI 31.1-37.9/100,000), outranked by ischaemic heart disease, stroke and chronic obstructive pulmonary disease.[28] Meta-analysis by Fine et al. in 1995 reported mortality rate of 13.6% in hospitalised patients (n=25,629, n=84 studies), with a significant rise to 36.5% for those admitted to intensive care units (ICUs) (n=788, n=13 studies).[29] In 2012, Welte et al. reviewed published European studies and reported a case fatality range of 5.6-43% for hospitalised patients, with 22-48% for those requiring admission to ICU.[18] The latest BTS National CAP Audit 2018/19 reported the lowest 30-day mortality in the past decade

at 10.4%.[30] Prior to this audit cycle, there was a steady decline in inpatient mortality from 20.2% to 17.7% between 2009/10-2014/15.

Factors associated with increased 30-day mortality include older age, ICU admission, presence of comorbidities (including neoplastic disease, chronic pulmonary disease, congestive heart failure, coronary artery disease, neurological disease, liver disease, renal disease, dementia and diabetes), bacteraemia, pneumococcal aetiology disease, lifestyle factors (smoking and alcohol abuse), admission from nursing home, multilobar involvement, and the development of incident cardiac complications (myocardial infarction, new or worsening heart failure, and new or worsening arrhythmia).[31–37]

Mortality rate appear to be the highest within the first few days after hospitalisation, irrespective of disease severity.[31] Two studies have reported early deaths in 30.3%- 38.6% at two and three days of admission respectively.[38,39] Independent predictors of early death in these studies include increased age, altered mental status, multilobar pneumonia, shock on admission, mechanical ventilation on admission, pneumococcal bacteraemia and discordant antibiotic therapy. Patients admitted with CAP have also been shown to have decreased long-term survival. In a Dutch study, patients hospitalised with CAP had a significantly higher long-term mortality than age and sex-matched controls (RR 3.6, $p<0.001$) with the highest annual mortality observed within the first 3 years of follow-up.[40] Similar increased long-term mortality was seen compared to patients admitted for another reason in 2 further studies at 5 and 7 years of follow-up in US and this effect remained significant after adjustment for age and comorbidities; OR 5.6, 95% CI 2.8-11.2 and HR 1.4, 95% CI 1.2-1.5 respectively.[41,42] Late deaths are more likely to be related to comorbid illness such as malignancy, COPD, or cardiovascular

disease compared to early deaths which are due to infectious conditions (pneumonia, sepsis or bacteraemia), respiratory failure, and cardiac complications.[43–45]

A higher mortality was observed in patients with dual bacterial and viral infection, compared with those without dual infection; OR 2.1, 95% CI 1.32-3.31.[19]

1.7 Morbidity

The majority of patients (~90%) admitted for community-acquired pneumonia survive to hospital discharge.[30] However, little is known about the morbidity related to recovery from pneumonia. Readmission to hospital after an episode of CAP is common. An unpublished meta-analysis of 60 studies estimated the pooled 30-day readmission rate to be 10% with 31% of readmissions due to pneumonia-related reasons.[46] The BTS National CAP Audit 2018/19 reported the 30-day readmission following CAP has increased from 10.5% in 2009 to 14.6% in 2018 in the UK.[30] Whilst it is recognised that patients consult healthcare providers following an admission for CAP, the full scale of the problem is unknown, especially with minimal data on primary care utilisation. A small study of 108 working age adults found 59.2% consulted primary care and 12% attended emergency department within 4 weeks; persistence of respiratory symptoms accounted for majority of these consultations.[47]

Previous studies on LRTI consultations not requiring hospital admission found that a prior consulting behaviour was a strong predictor of further consultation.[48,49] The patient cohorts in these primary care studies are mostly different compared to patients hospitalised with CAP, often involving adults with self-limiting RTIs in whom the challenge is the avoidance of overuse of antibiotics and managing patient expectation. Taking this

into consideration, the reasons for prior consulting behaviour emerging as a strong predictor of further consultation were speculated to be due to unrealistic expectations of the resolution of symptoms and a heightened consulting habit. [49]

Patients are believed to have achieved 'clinical cure' or recovered from pneumonia when there is resolution of signs and symptoms related to pneumonia without recurrence.[50] Radiographic clearance of CAP varies between 35.1% at 3 weeks (in patients >70 years) to 66.7% at 4 weeks.[51,52] Bruns et al. reported physician-based clinical cure in 88.9% at 28 days after hospitalisation for mild to moderate CAP, though radiological resolution was seen in 68.4% and symptoms were completely resolved in only 41.7%, highlighting the discordance between physician rated clinical cure, radiographic resolution and patient reported symptoms.[53]

In a systematic literature review of patient reported outcome measures in CAP, Pick et al. found that up to 70% of patients continue to report at least one symptom 4 weeks post-discharge; the commonest symptom being fatigue, followed by cough and dyspnoea.[54] Functional impairment was reported in 18-51% of patients at four weeks post-discharge with a median time to return to normal activities of 15-28 days. One study found 16.3% of survivors at 6 weeks after hospitalisation for CAP required a change of residence on discharge, indicating a greater level of dependency.[55] These studies suggest that the full long-term burden of adverse health outcomes after CAP is likely to be higher than measures of symptoms resolution alone.[56] It is important to note that an episode of pneumonia may be a marker for frailty or increased susceptibility to illness from non-pneumonia related factors.[57]

1.8 Thesis objectives

In summary, a better understanding of the morbidity after CAP is necessary to develop and implement appropriate interventions to improve the long-term outcomes of patients hospitalised with CAP. In this thesis, there are three main research aims to improve our understanding on the morbidity after CAP:

1) To describe the primary care consultations after CAP and the reasons for these consultations
2) To determine the incidence of, and risk factors for developing cardiac complications
3) To determine the role of tobacco smoking in recurrent hospitalisation for CAP

1.9 Outline of chapters

The following is a brief overview of subsequent chapters in this thesis:

Chapter 2: Methods for studies using Clinical Practice Research Datalink (CPRD), linked to Hospital Episode Statistics (HES)

This chapter gives an overview of the databases used for three studies in this thesis, the study population and how the variables that are used across studies are defined.

Chapter 3: Primary care consultations following hospitalisation for pneumonia

This study addresses the gap in knowledge about the burden on primary care following hospitalisation for pneumonia with specific objectives of:

- determining the rate and predictors of consultation
- exploring reasons for primary care consultations and hospital readmissions
- investigating further antibiotic prescription at consultation.

Chapter 4: Cardiac complications following community acquired pneumonia: A systematic review and meta-analysis

This chapter summarises the available evidence on cardiac complications, a major morbidity following CAP. Key objectives were to determine the:

- short- (<30 days), medium- (90 days) and long-term (>1 year) effect of CAP on developing incident cardiac complications
- risk factors and biomarkers associated with developing cardiac complications
- mortality

Chapter 5: Matched cohort study of cardiac complications after hospitalisation for pneumonia.

Using the background information from Chapter 4, the aims of this study were to determine the incidence of cardiac complications after hospitalisation for pneumonia at 30 days, 90 days and 1 year, and the associated risk factors, when compared to the general population in a matched cohort study.

Chapter 6: Effect of tobacco smoking on the risk of developing community acquired pneumonia: A systematic review and meta-analysis

This chapter summarises the available evidence on tobacco smoking and passive smoke exposure as a risk factor for developing CAP. Key objectives were to:

- determine the effect of tobacco smoking and passive smoke exposure on the risk of developing CAP in adults
- determine the strength of the association
- to examine whether there is a 'dose-response' association between amount of tobacco smoked and the risk of developing CAP.

Chapter 7: Tobacco smoking is an important modifiable risk factor for recurrent hospitalisation with pneumonia

The primary objective of this study was to determine incidence of recurrent hospitalisation with pneumonia in England, another major morbidity associated with CAP. Using the background information from Chapter 6, this chapter explores the association of tobacco smoking as a potentially modifiable risk factor for recurrent hospitalisation with pneumonia was explored and determines the proportion of current smokers admitted with index pneumonia who were offered stop smoking interventions.

Chapter 8: Co-infection in critically ill patients with COVID-19: A retrospective multicentre cohort study from England

This chapter describes a study conducted during the first-wave of COVID-19 pandemic. The primary objective was to determine the proportion of laboratory proven co-infection in critically ill adults with COVID-19 infection in England. Secondary objectives were to:

- to describe the organisms
- the characteristics of patients with co-infection
- the antibiotic susceptibilities of identified bacteria.

Chapter 9: Conclusions and future research

This chapter summarises the main findings of this thesis and describes the implications to clinicians and policy makers. This chapter concludes with future research recommendations.

Chapter 2

Chapter 2 Methods for studies using Clinical Practice Research Datalink (CPRD), linked to Hospital Episode Statistics (HES)

This chapter describes the data sources, in addition to the definitions of exposures, outcomes and covariates used in the studies in this thesis. It also provides an overview of the study designs and methods used in each study. Detailed methods for individual studies are described in subsequent chapters.

2.1 Ethical approval

Ethical approval was provided by the Medicines and Healthcare products Regulatory Agency (MHRA) Independent Scientific Advisory Committee (ISAC); study protocol number: 18_178A (Appendix 1).

2.2 Data sources

Anonymised data were used from four sources: primary care, and linked data to secondary care, death registration data and deprivation data.

2.2.1 Primary care data

The Clinical Practice Research Datalink (CPRD) is a real-world UK government research service which collects anonymous patient data from a network of general practices across the England, Scotland, Wales and Northern Ireland. It is now one of the world's largest databases of longitudinal primary care electronic health records (EHRs). CPRD is jointly funded by the MHRA and the National Institute for Health Research (NIHR), as part of the Department of Health and Social Care. CPRD collects fully-coded patient EHR from practices using Vision® (CPRD GOLD) or EMIS Web® (CPRD Aurum) software systems with some differences in the structure and clinical coding in these two systems. Following ethical approval by MHRA Independent Scientific Advisory Committee (ISAC) (study

protocol number: 18_178A), access to the CPRD GOLD July 2018 file was provided. This file contained 15.5 million patients (including those who transferred out of practice and deceased), who were broadly representative of the UK population with respect to age, sex and region. Of these, 2.3 million patients were actively contributing data; this covered 3.6% of the total UK population. Data were available from 738 practices; 272 actively contributing practices. All patients registered with a participating practice are included in the dataset, with the exception of those who have opted-out of data sharing.

2.2.1.1 Data quality

Primary care data quality is variable as data are entered during routine consultations, not for the purpose of research. Therefore, comprehensive data quality checks were undertaken before conducting the studies in this thesis. In order to select research-quality patients and periods of quality data recording, there are two measures which are recommended to be used by the CPRD: acceptability for patients and up to standard (UTS) time for practices. The former is based on registration status, recording of events in the patient record, and valid age and gender; patients are labelled as 'acceptable' for use in research by a process that identifies and excludes patients with non-continuous follow up or patients with poor data recording that raises suspicion of the validity of the patients' record. The latter, UTS date is the date at which data in the practice is considered to have continuous high-quality data fit for use in research. This date is calculated for each participating practice, based on the continuity of data recording and the number of recorded deaths.

2.2.1.2 Data supplied by CPRD

CPRD provides data to researchers in several file types which separates information into different categories. The file types used in this thesis include patient, practice,

consultation, clinical, additional clinical details and therapy (**Table 2-1**). Patients are assigned a unique identifier which enables their records to be linked across the files and a consultation identifier which allows events from the same consultation to be linked.

Table 2-1: Data files supplied by CPRD and used in this thesis

File type	Information	Example of contents
Patient	Demographics and registration status of patients	Patient identifier, month and year of birth, registration date with the practice, death date, transfer out of practice date
Practice	Practice administrative data	Practice identifier, geographical region, date practice became 'Up to standard' (UTS) i.e. when data from practice were deemed to be of research quality, last data collection date
Consultation	Administrative information about the consultation	Date of clinical event, date of data entry, type of consultation (e.g. clinic, follow-up visit, emergency consultation, telephone consultation, discharge details, administration) and duration of consultation
Clinical	Clinical data regarding medical history including diagnoses, signs and symptoms	Date of clinical event, date of data entry, the CPRD medical code for the chosen Read code, additional details identifier*, entity type
Additional clinical details	Specific data about a clinical event	Type of information held (e.g. smoking status, alcohol consumption), called an 'entity', specific clinical details relating to that entity
Therapy	Information about therapies including medications and appliances	The CPRD product code for the medication, British National Formulary code, quantity of product, dose, pack size, number of days prescribed

Adapted from Herrett et al.[58]

*Allows a link to be made between a Read code in the 'clinical file' to additional details held in the 'additional clinical details' file.

2.2.2 Data linkage

English practices contributing to CPRD data can be linked to other established non-primary care data such as hospitalisation data from Hospital Episode Statistics (HES), death registration data from Office for National Statistics (ONS) and deprivation data (**Table 2-2**). These linkages were available for approximately 50% of contributing CPRD GOLD practices in the UK. Data linkages are not available for CPRD practices in the rest of

the UK due to different operating systems similar to HES in England; The Scottish Morbidity Record, The Patient Episode Database for Wales and The Northern Ireland Hospital Statistics Dataset.

HES Admitted Patient Care (HES APC) data contain details of all admissions to NHS hospitals in England.[59] Hospitalisations, also known as 'spells' in HES refer to the total period of inpatients hospital stay from admission to discharge, therefore includes information on the admission and discharge dates. Each spell may contain several 'episodes', a time-period which corresponds to when a patient is in the continuous care of a consultant and for each episode, there may be up to 20 diagnoses recorded. The primary diagnosis i.e. the first diagnosis recorded during the first episode of the patient care was used as the reason for the patients' admission in this thesis. Diagnostic data recorded in HES are coded using International Classification of Diseases, Tenth Revision (ICD-10).

Death registration data contains data from the Office for National Statistics (ONS) and includes information on the date of death and causes of death coded using ICD-10.

The Index of Multiple Deprivation (IMD) is one the most commonly used measures of deprivation and data are provided in quintiles; score of 1 (least deprived) -5 (most deprived). A composite index is calculated by combining a number of indicators covering seven domains of material deprivation: housing, employment, income, access to services, education and skills, crime and living environment.[60] The 2015 English IMD (Set 17) was used in this thesis and data were linked to CPRD primary care data through the practice postcode. The practice postcode is mapped to Lower Super Output Areas (LSOA), small-

level geographic regions based on census geography with a minimum size of 1,000 residents and 300 households, and an average of 1,600 residents.[61]

Table 2-2: Data sources linked to CPRD primary care records used in this thesis.

Linkage	HES APC	Death Registration	Deprivation
Type of resource	Hospitalisation data for inpatients	Date and cause of death register	Socioeconomic status
Who is included?	Patients with hospitalisations for any cause	People who die in England and Wales	Lower super output area levels
Geographic regions covered by linkage	England	England and Wales	England, Wales, Scotland and Northern Ireland
Period of linkage for this thesis	01/04/97 – 30/11/18	02/01/98– 14/01/19	-
Examples of data available in linked dataset	Diagnoses, procedures	Date and cause of death, including underlying and secondary causes.	Index of Multiple Deprivation (IMD)

2.2.3 Generalisability and validity of data

CPRD data are broadly representative of the UK population with respect to age, sex and ethnicity.[58] CPRD has been widely used for epidemiological research for a range of conditions. A systematic review of 212 publications investigating the validation of 183 diagnoses recorded in the database found a high data validity; median proportion of cases with a confirmed diagnosis by either internal (e.g. manual review of records including free-text or diagnostic algorithm using symptoms/signs, prescriptions for disease-specific drugs and/or confirmatory test results) or external validation (e.g. by requesting additional information from GP comparison of rates with a non-CPRD, UK-

based data source) of 89% overall and 88% for respiratory system diagnoses in particular.[62]

An important external influence that could have a potential impact on the data quality in CPRD is the introduction of the Quality and Outcomes Framework (QOF) in 2004. The QOF is a voluntary annual reward and incentive programme for all GP surgeries in the UK, which financially rewards GPs for providing high quality care to their patients.[63] The QOF has resulted in considerable improvement in the recording of key lifestyle variables particularly smoking status and offering cessation advice.[64,65]

HES APC has universal coverage, providing an unselected sample of hospital admissions. In comparison to CPRD, HES is less extensively validated. Clinical coders rely on the quality and detail of completed discharge summaries to enter data consistently using ICD-10 codes.[66] Since the introduction of Payment by Results in 2003/04, an initiative to direct health-care funding based on coding data, there has been an increase in the number of diagnostic codes used and improvement in diagnostic accuracy.[67] The average inaccurate diagnosis and procedure coding has reduced from 16.5% in 2007/08 to 11.3% in 2009/10.[68] Roughly a third of ICD-10 coded cases of pneumonia within HES lack radiographic evidence of pneumonia and would strictly be considered cases of non-pneumonic LRTI.[30] The vast majority of these patients are nevertheless treated clinically as having pneumonia and inclusion of these patients in the analysis reflects real-world practice.

2.3 Study population

Adults aged ≥18 years with the first episode of hospitalisation for pneumonia (index date) recorded in HES between 1 July 2002 and 30 June 2017 were included. Patients were excluded if they a) did not have data that met the minimum quality criteria for use in research b) had less than a year of time registered to practice before admission or c) were admitted for at least a day in the 10 days preceding the index admission (hospital-acquired pneumonia identified from HES).

2.4 Building the dataset: Definition of key variables

This section describes the key variables used throughout the research. Other variables used in the three studies will be described in the individual chapters.

2.4.1 Definition of pneumonia

The focus of this research was on pneumonia. Pneumonia was defined based on J12- J18 ICD-10 codes recorded as the primary code for the first episode of hospitalisation in the HES dataset (**Table 2-3**). The 'epidemiological year' definition of July- June was used as the unit of time in order to avoid the winter peak of pneumonia traversing two calendar years.

Table 2-3: ICD-10 codes for pneumonia

ICD-10 code	Description
J12	Viral pneumonia, not elsewhere classified
J13	Pneumonia due to *Streptococcus pneumoniae*
J14	Pneumonia due to *Haemophilus influenzae*
J15	Bacterial pneumonia, not elsewhere classified
J16	Pneumonia due to other infectious organisms, not elsewhere classified

J17	Pneumonia in diseases classified elsewhere
J18	Pneumonia, unspecified organism

2.4.2 Definition of covariates in CPRD

Age

Age was calculated as year of admission – year of birth. Age was categorised into five categories; 18-49, 50-64, 65-74, 75-84, ≥85

Gender

Patients were included in the analyses if they were coded as male or female. Three patients with an indeterminate gender were excluded.

Smoking status

Smoking status were divided into three categories; never smokers, ex-smokers and current smokers. If patients had more than one record for smoking status, the most recent record of smoking status was used. Never smokers were reclassified to ex-smokers if they had any record of smoking recorded in their entire clinical record entered on CPRD prior to study entry. Read code lists for smoking status were developed using validated medical Read codes (Appendix 2).[69,70]

Alcohol consumption

Alcohol consumption was divided into five categories; non-drinkers, former drinkers, occasional drinkers, current moderate drinkers (≤14 units/ weekly) and current heavy drinkers (>14 units/ weekly). Similar to smoking status, the most recent record of alcohol consumption was used if there were more than one record available. Non-drinkers were reclassified to former drinkers if they had any record of drinking recorded in their entire clinical record entered on CPRD prior to study entry. Read code lists for alcohol consumption were developed using validated medical Read codes (Appendix 2).[70,71]

Charlson Comorbidity Index score

The Charlson Comorbidity Index (CCI) is a weighted index which takes into account the number and seriousness of comorbid disease. Charlson et al. developed this index in a cohort of 559 hospitalised patients and the 1-year mortality rates for the different scores were determined.[72] The index was validated in a second cohort of 685 patients, where the ability to predict risk of death from comorbid disease during a 10-year follow up was tested. With every rise in the CCI score, there was a stepwise increase in the cumulative mortality attributable to comorbid disease. The CCI is calculated using 15 conditions including myocardial infarction (MI), congestive cardiac failure (CCF), peripheral vascular

disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, liver disease, diabetes, hemiplegia, renal disease, any tumours, haematological malignancy and acquired immune deficiency syndrome (AIDS). Each of these comorbidities is assigned a weighted score and the sum of the scores is an indicator of the overall disease burden. Read code lists for CCI were developed using validated medical Read codes (Appendix 2).[70,73]

Comorbid conditions of interest

In addition to CCI, Read codes lists were developed for specific comorbid conditions of interest including chronic obstructive lung disease (COPD), asthma, cardiac diseases excluding CCF and MI (e.g. hypertension, arrhythmias, valvular heart disease, conduction disorder of the heart, pericarditis, myocarditis) and cognitive impairment (Appendix 2).

Chapter 3

Chapter 3 Primary care consultations following hospitalisation for pneumonia

3.1 Introduction

The majority of patients (>85%) admitted for community-acquired pneumonia survive to hospital discharge.[30] However, little is known about the morbidity related to recovery from pneumonia. A systematic literature review of patient reported outcome measures in CAP found limited research suggesting that up to 70% of patients continue to report at least one symptom four weeks post-discharge; the commonest symptom being fatigue, followed by cough and dyspnoea. Functional impairment is reported in 18-51% of patients at four weeks post-discharge with a median time to return to normal activities of 15-28 days.[54]

Readmission to hospital is also common. A meta-analysis (n=60 studies) estimated the pooled 30-day readmission rate to be 10% with 31% of readmissions due to pneumonia-related reasons.[46] In the UK, 30-day readmission following CAP has increased from 10.5% in 2009 to 14.6% in 2018.[30] In contrast, the impact on primary care is much less well understood. In a small exploratory study (n=108) of working age adults (<65 years old) discharged from hospital following admission for CAP, 59% consulted primary care within 28 days of discharge, suggesting a potentially important burden to the NHS that is currently unrecognised.[47]

The aim of this study was to address the gap in knowledge about the burden on primary care following hospitalisation for pneumonia with specific objectives of (1) determining the rate and predictors of consultation, (2) exploring reasons for primary care consultations and hospital readmissions, and (3) investigating further antibiotic prescription at consultation.

3.2 Methods

3.2.1 Study population and follow-up

Adults aged ≥18 years with the first episode of hospitalisation for pneumonia (index date) recorded in HES (data from NHS hospitals in England) between 1 July 2002 and 30 June 2017 were included. The 'epidemiological year' definition of July- June was used as the unit of time in order to avoid the winter peak of pneumonia traversing two calendar years. Pneumonia was defined based on J12- J18 ICD-10 codes recorded as the primary code for the first episode of hospitalisation. Patients were excluded if they a) did not have data that met the minimum quality criteria for use in research b) had less than a year of time registered to practice before admission or c) were admitted for at least a day in the 10 days preceding the index admission (identified from HES). Patients were followed up from day one after the date of discharge from hospital to either the first primary care consultation, end of data collection (30 days), date of transfer out of practice, date of last data collection for the practice or date of death, whichever came first.

3.2.2 Definitions

Primary care consultation was considered to have occurred if medical Read codes were recorded after the date of discharge from hospital; administration-related codes were excluded to capture face-to-face consultations.[74,75] If there were multiple Read codes recorded in a day per patient, this was counted as a single episode of consultation. Validated codelists were used for pneumonia, smoking status, alcohol consumption, Charlson Comorbidity Index and specific co-morbidities of interest.[70,76,77] In addition to the common reasons for consultations, namely respiratory, digestive, genitourinary and cardiac disorders, constitutional symptoms and cognitive disorder were categorised

according to Read codes. These category codes were developed for this study by a specialist trainee in respiratory medicine, a consultant in respiratory medicine, a geriatrician and an epidemiologist, and reviewed by an academic general practitioner. Within the 'respiratory' category, a subset of 'only pneumonia Read codes' was developed to determine the proportion of patients who consulted directly due to pneumonia. Read codes for antibiotics were categorised according to the British National Formulary (BNF) listing in Section 5.1 (Antibacterial drugs), excluding anti-tuberculosis and anti-leprotic drugs.

3.2.3 Patient involvement

The study concept and design were discussed with members of the Nottingham Lung Infection PPI group from inception. The group, comprising of patients previously treated for CAP, actively contributed towards identifying the issue of primary care consultation after hospitalisation for pneumonia as important and the need to develop the research question and relevant outcome measures; including "Who are more likely to consult?", "Why do they consult" and "Are additional antibiotics prescribed at consultation?". The group received regular updates on the progression of the research protocol development, ethics review and study conduct via regular PPI meetings. Findings of the study were discussed with PPI members and the authors have disseminated pre-publication study results via conference abstract presentations.

3.2.4 Statistical analysis

Age was fitted as a categorical variable following likelihood ratio test (age categories: 18-49, 50-64, 65-74, 75-84, ≥85). The 2015 English Index of Multiple Deprivation (IMD) was used as composite measure of material deprivation at the patient level.[78] 'Time to

consultation' was measured from day one after discharge from hospital to the first consultation at primary care. Based on the first episode of consultation per patient, rates of consultation per 100 person-days for ≤7 days and ≤30 days were determined. Characteristics of adults who consulted were compared to those who did not consult. A predictive modelling approach was used where important predictors of consultations were determined from published literature on consultations for acute lower respiratory tract infection (LRTI) based on a postulated similarity between pneumonia and non-pneumonic acute LRTI in this regard.[49] There were missing data in smoking status (2.9%), alcohol consumption (15.1%) and IMD score (0.1%). The pattern of missing data for smoking status and alcohol consumption are shown in **Table 3-1**.

Table 3-1: Pattern of missing data for smoking status and alcohol consumption

Percentage of data	Missing Pattern	
	Smoking status	Alcohol status
85%	1	1
13%	1	0
2%	0	0
<1%	0	1
100%		

Legend: 0 Missing data, 1 Non-missing data

Multiple imputation using chained equations was performed with 10 imputed datasets for smoking status and alcohol consumption respectively, under a missing at random (MAR) assumption in line with previous published studies using CPRD data and are reported as per the suggested guidelines by Sterne et al.[79–83]

Univariate and multivariate competing-risks regression analyses were used with death and readmission as competing events. Univariate analyses were conducted to investigate the association between primary care consultation and each variable (age, gender,

smoking status (never smoked, ex-smokers, current smokers), alcohol consumption (non-drinker, former drinker, occasional drinker, moderate drinker (≤14 units/week), heavy drinker (>14 units/week)), length of hospital stay (≤3, 4-7, >7 days), previous primary care consultations in the past year prior to admission for pneumonia (<5, 5-15, >15 consultations), IMD quintile (score of 1 (least deprived) -5 (most deprived), unknown), practice region (West Midlands, North West, Yorkshire and the Humber, East Midlands, North East, East of England, South West, South Central, London, South East Coast; West Midlands was selected as the reference region for analyses as it was a region representative of England by population size, age and gender[84]), presence of comorbidities (measured using Charlson Comorbidity Index and specific comorbidities of interest: chronic pulmonary obstructive disease (COPD), asthma, chronic lung disease (excluding COPD and asthma) congestive cardiac failure (CCF), myocardial infarction (MI), other cardiac diseases (excluding CCF and IHD), malignancy, chronic renal disease, cognitive impairment, cerebrovascular disease, diabetes mellitus, liver disease). Variables that were considered associated in the univariate analyses ($p<0.05$) were included in a multivariable backward logistic regression model with imputed data; age and sex were *a priori* variables. Charlson Comorbidity Index and specific comorbidities of interest were included in separate multivariate models. Sensitivity analysis was performed excluding previous consulting behaviour.

The proportions for reasons of consultations were calculated for all patients who consulted, with sub-analyses for those who consulted before readmission or death. The top 20 reasons for hospital readmission were also determined. In addition, the number of antibiotic prescriptions, frequency of antibiotic courses (multiple antibiotics prescribed at a single consultation were counted as a single 'course') and the type of antibiotics prescribed at primary care consultation were also examined. Univariate and multivariate

logistic regression analyses were performed to investigate predictors of antibiotic prescription at consultation. Statistical analyses were performed using StataMP/ 15.1.

3.3 Results

Over the 15-year study period, there were 215,828 patients admitted to hospital with ICD-10 codes for pneumonia (Fig 3-1) of whom 17,928 had hospital acquired pneumonia and 37,442 (20.6%) died in hospital. After excluding remaining patients who did not have data that met the minimum quality criteria for use in research and patients who did not have at least a year of time registered to practice (n=87,773), the study cohort comprised 56,396 patients.

Fig 3-1: Flowchart of the study population

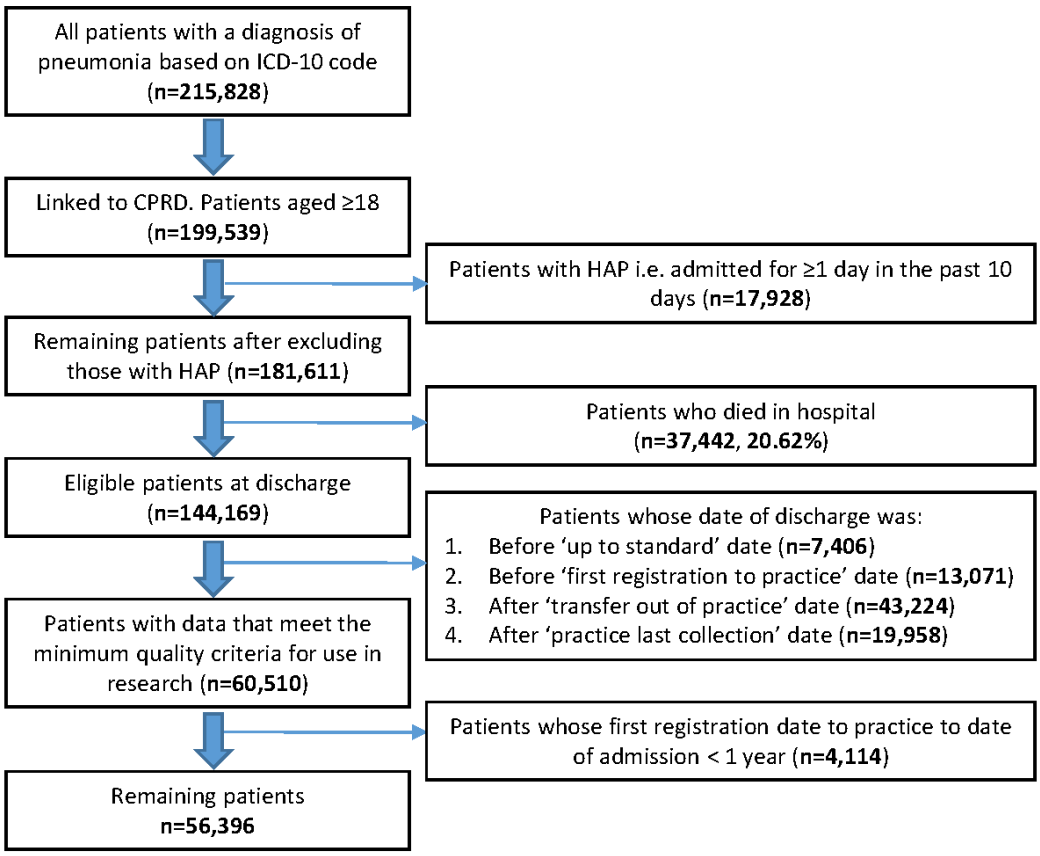


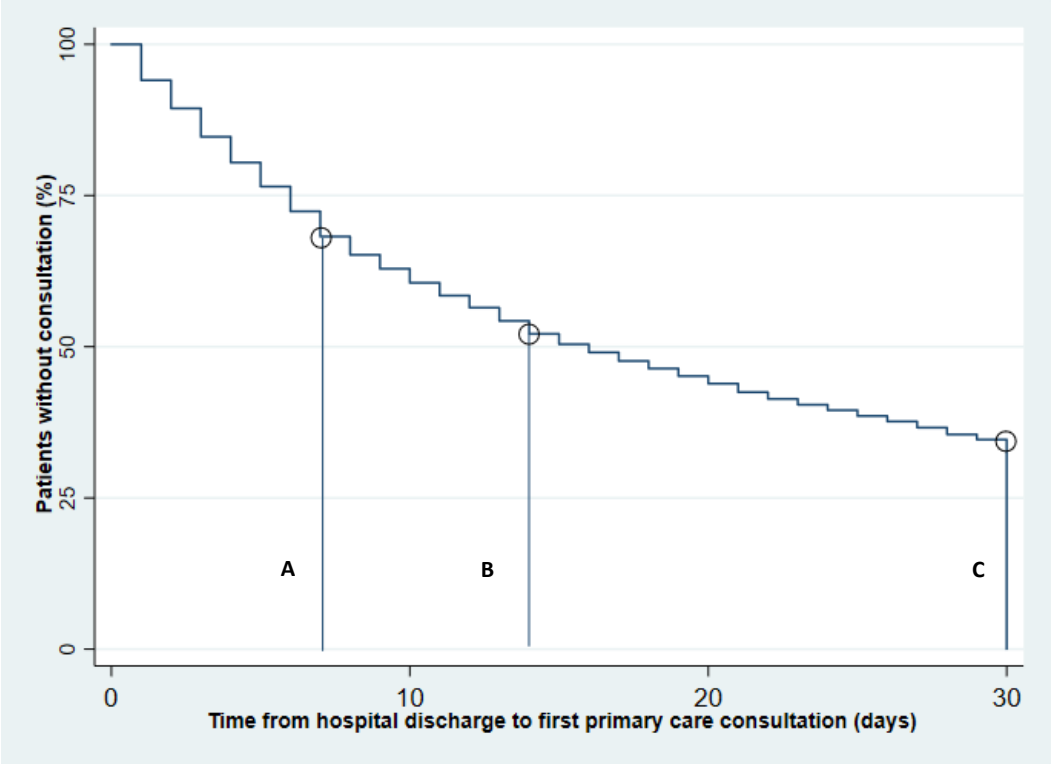
Table 3-2 shows the characteristics of the study population. Median age of the study cohort was 75 years (range 18-108 years; interquartile range (IQR): 61-84 years) and 49.7% were male. During the 30-day follow-up, 16% (n=9,051) were readmitted to hospital and 6.1% (n=3,446) died after discharge from hospital.

Table 3-2: Characteristics of the overall study population

	Overall study population n (%)	
Number of patients	56,396	
Age		
18-49	8208	(14.6)
50-64	8830	(15.7)
65-74	10499	(18.6)
75-84	15317	(27.2)
≥85	13542	(24.0)
Gender		
Male	28002	(49.7)
Female	28394	(50.4)
IMD (patient-level)		
1 (least deprived)	10596	(18.8)
2	11407	(20.2)
3	11909	(21.1)
4	11263	(20.0)
5 (most deprived)	11171	(19.8)
Unknown	50	(0.1)
Practice region		
West Midlands	6990	(12.4)
North West	9855	(17.5)
Yorkshire & The Humber	1926	(3.4)
East Midlands	1294	(2.3)
North East	1454	(2.6)
East of England	5589	(9.9)
South West	7541	(13.4)
South Central	7031	(12.5)
London	7114	(12.6)
South East Coast	7602	(13.5)
Charlson Index		
0	13636	(24.2)
1	12290	(21.8)
2	9912	(17.6)
3	7777	(13.8)
4	5096	(9.0)
≥5	7685	(13.6)

Primary care consultation occurred in 27.7% (n=15,626 patients) and in 55.9% (n=31,542 patients) within 7 days and 30 days of discharge respectively (**Fig 3-2**).

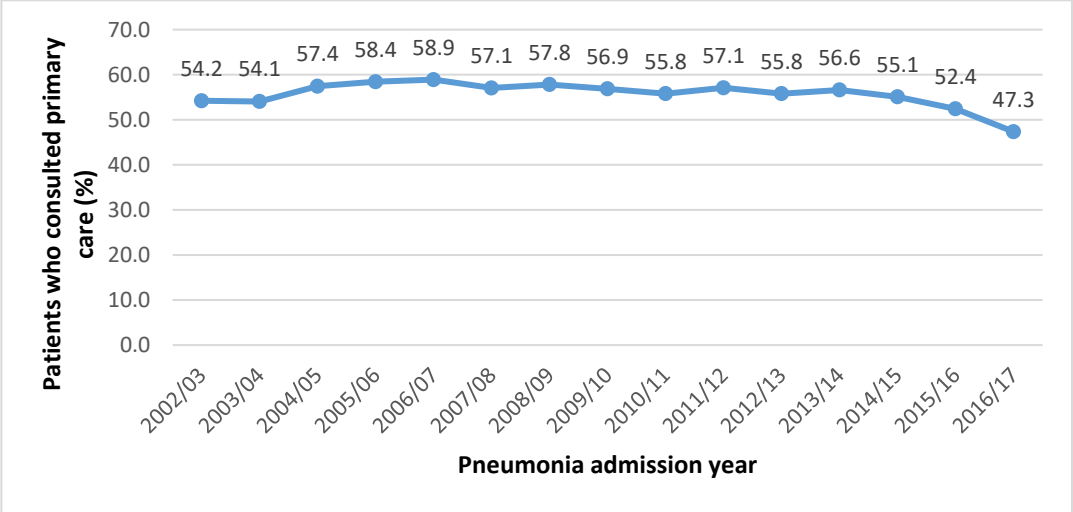
Fig 3-2: Kaplan- Meier plot of time to first consultation



Legend: Vertical line A- 7 days, B- 14 days and C- 30 days.
The highest consultation occurred within 7 days (27.7%), after which there was a decline in consultation (14 days: 41.4%, 30 days: 55.9%)

The 30-day consultation proportion gradually increased from 54.2% in 2002/03 to a peak of 58.9% in 2006/07. This remained relatively stable until 2013/14 (56.6%) after which there was a steady fall to 47.3% in 2016/17 (**Fig 3-3**). The rate of first consultation was highest within 7 days of hospital discharge at 4.7 per 100 person-days and declined to 3.3 per 100 person-days within 30 days of hospital discharge. Of those who consulted within 30 days, 47.7% (n=15,056) consulted two or more times.

Fig 3-3: Trend of primary care consultation over the 15-year study period



3.3.1 Factors associated with consultation

The strongest predictor of consultation was previous consultation behaviour; specifically having consulted >15 times in the year prior to the index admission for pneumonia (adjusted sHR 8.98, 95% CI 6.42 to 12.55) (**Table 3-3**). Other factors independently associated with a higher probability of consultation were age 50-74 years compared to 18-49 years, current and ex-smoking status compared to never smokers, length of hospital stay of between 4-7 days compared to ≤3 days, Charlson Comorbidity Index score ≥3 and pre-existing comorbid diseases; COPD, asthma, congestive cardiac failure, myocardial infarction, other cardiac diseases and diabetes mellitus. Geographical variation was observed with the lowest probability of consultation in the South East Coast compared to West Midlands. Over the course of the 15-year study period, lower probability of consultation was noted from 2009/10 onwards compared to 2002/03-2004/05. Other important factors independently associated with lower probability of consultation were age ≥85 years and patients who are more deprived. Gender and alcohol consumption were not independently associated with consultation.

Table 3-3: Univariate and multivariate competing-risks regression analyses investigating the predictors of primary care consultation after hospitalisation for pneumonia in the first 30 days after discharge.

	Did not consult n (%)	Consulted n (%)	Univariate CRR sHR (95% CI)	Multivariate CRR sHR (95% CI)	p value
Number of patients	24854	31542			
Age					
18-49	4017 (48.9)	4191 (51.1)	1.00 Reference	1.00 Reference	
50-64	3755 (42.5)	5075 (57.5)	1.18 (1.13-1.23)	1.08 (1.04-1.13)	*<0.001
65-74	4277 (40.7)	6222 (59.3)	1.24 (1.19-1.28)	1.08 (1.03-1.12)	*<0.001
75-84	6459 (42.2)	8858 (57.8)	1.21 (1.16-1.25)	1.03 (0.99-1.07)	0.161
≥85	6346 (46.9)	7196 (53.1)	1.10 (1.06-1.14)	0.95 (0.91-0.99)	*0.018
Gender					
Male	12277 (43.8)	15725 (56.2)	1.00 Reference	1.00 Reference	
Female	12577 (44.3)	15817 (55.7)	0.99 (0.96-1.01)	0.99 (0.97-1.01)	0.32
Smoking status					
Never	8036 (45.5)	9634 (54.5)	1.00 Reference	1.00 Reference	
Ex	5970 (42.3)	8149 (57.7)	1.08 (1.05-1.11)	1.03 (1.00-1.06)	*0.03
Current	9897 (43.1)	13061 (56.9)	1.06 (1.03-1.09)	1.03 (1.00-1.06)	*0.027
Unknown	951 (57.7)	698 (42.3)	-		
Alcohol status					
Non-drinker	5559 (44.2)	7016 (55.8)	1.00 Reference		
Former drinker	1164 (41.1)	1667 (58.9)	1.08 (1.03-1.14)		
Occasional drinker	3276 (42.4)	4454 (57.6)	1.04 (1.00-1.08)		
Moderate drinker	7717 (42.4)	10499 (57.6)	1.03 (1.00-1.06)		
Heavy drinker	2896 (44.2)	3663 (55.8)	0.98 (0.94-1.02)		

Unknown	4242	(50.0)	4243	(50.0)	-				
CAP admission year									
2002/03-2004/05	3296	(44.6)	4094	(55.4)	1.00	Reference	1.00	Reference	
2005/06-2006/07	2650	(41.3)	3764	(58.7)	1.09	(1.05-1.14)	1.03	(0.99-1.08)	0.144
2007/08-2008/09	3387	(42.5)	4576	(57.5)	1.05	(1.01-1.09)	0.98	(0.94-1.02)	0.256
2009/10-2010/11	4157	(43.7)	5357	(56.3)	1.03	(0.98-1.07)	0.95	(0.91-0.99)	*0.008
2011/12-2012/13	4416	(43.6)	5717	(56.4)	1.04	(1.00-1.08)	0.95	(0.91-0.99)	*0.014
2013/14-2014/15	3984	(44.1)	5042	(55.9)	1.04	(1.00-1.08)	0.95	(0.91-0.99)	*0.015
2015/16-2016/17	2964	(49.8)	2992	(50.2)	0.88	(0.84-0.93)	0.82	(0.79-0.87)	*<0.001
Length of stay									
≤3	7694	(44.9)	9455	(55.1)	1.00	Reference	1.00	Reference	
4-7	6351	(42.1)	8743	(57.9)	1.07	(1.04-1.10)	1.04	(1.01-1.07)	*0.019
>7	10809	(44.8)	13344	(55.2)	1.03	(1.01-1.06)	1.00	(0.97-1.02)	0.852
Primary care consultations in the previous year									
0	358	(91.1)	35	(8.9)	1.00	Reference	1.00	Reference	
<5	1108	(61.3)	700	(38.7)	5.31	(3.77-7.48)	5.11	(3.63-7.21)	*<0.001
5-15	4039	(50.7)	3931	(49.3)	7.27	(5.20-10.16)	7.05	(5.04-9.87)	*<0.001
>15	19349	(41.9)	26876	(58.1)	9.30	(6.66-12.99)	8.98	(6.42-12.55)	*<0.001
IMD (patient level)									
1 (least deprived)	4617	(43.6)	5979	(56.4)	1.00	Reference	1.00	Reference	
2	5038	(44.2)	6369	(55.8)	0.98	(0.94-1.01)	0.96	(0.93-0.99)	*0.019
3	5116	(43.0)	6793	(57.0)	1.01	(0.98-1.04)	0.99	(0.96-1.03)	0.585
4	5053	(44.9)	6210	(55.1)	0.95	(0.92-0.99)	0.93	(0.90-0.96)	*<0.001
5 (most deprived)	5002	(44.8)	6169	(55.2)	0.96	(0.93-0.99)	0.91	(0.88-0.94)	*<0.001

Unknown	28	(56.0)	22	(44.0)	0.73	(0.48-1.10)	0.78	(0.51-1.18)	0.237
Practice region									
West Midlands	2878	(41.2)	4112	(58.8)	1.00	Reference	1.00	Reference	
North West	4160	(42.2)	5695	(57.8)	0.97	(0.93-1.01)	0.98	(0.94-1.02)	0.245
Yorkshire & The Humber	857	(44.5)	1069	(55.5)	0.89	(0.84-0.95)	0.89	(0.83-0.95)	*<0.001
East Midlands	533	(41.2)	761	(58.8)	1.00	(0.92-1.07)	1.01	(0.93-1.09)	0.846
North East	568	(39.1)	886	(60.9)	1.05	(0.98-1.12)	1.05	(0.98-1.13)	0.154
East of England	2246	(40.2)	3343	(59.8)	1.03	(0.99-1.08)	1.04	(0.99-1.08)	0.12
South West	3268	(43.3)	4273	(56.7)	0.93	(0.89-0.97)	0.92	(0.89-0.96)	*<0.001
South Central	3116	(44.3)	3915	(55.7)	0.91	(0.87-0.95)	0.90	(0.86-0.94)	*<0.001
London	3492	(49.1)	3622	(50.9)	0.80	(0.77-0.84)	0.83	(0.79-0.86)	*<0.001
South East Coast	3736	(49.1)	3866	(50.9)	0.80	(0.77-0.84)	0.81	(0.77-0.85)	*<0.001
§ Charlson Comorbidity Index									
0	6590	(48.3)	7046	(51.7)	1.00	Reference	1.00	Reference	
1	5488	(44.7)	6802	(55.3)	1.10	(1.06-1.13)	0.99	(0.96-1.02)	0.562
2	4387	(44.3)	5525	(55.7)	1.11	(1.07-1.15)	0.98	(0.95-1.02)	0.42
3	3279	(42.2)	4498	(57.8)	1.18	(1.14-1.23)	1.04	(1.00-1.08)	*0.047
4	2078	(40.8)	3018	(59.2)	1.23	(1.18-1.28)	1.08	(1.03-1.13)	*0.001
≥5	3032	(39.5)	4653	(60.5)	1.28	(1.24-1.33)	1.14	(1.09-1.18)	*<0.001
Co-morbidities									
COPD	4666	(39.5)	7132	(60.5)	1.14	(1.12-1.17)	1.05	(1.01-1.08)	*0.003
Asthma	5351	(40.1)	7996	(59.9)	1.12	(1.09-1.15)	1.06	(1.03-1.08)	*<0.001
¥Chronic lung disease	391	(43.6)	505	(56.4)	1.00	(0.92-1.09)			
Congestive cardiac	2251	(39.8)	3397	(60.2)	1.15	(1.11-1.19)	1.14	(1.10-1.18)	*<0.001

failure								
Myocardial infarction	2125	(40.3)	3143	(59.7)	1.12	(1.08-1.17)	1.10 (1.06-1.15)	*<0.001
#Other cardiac diseases	9755	(41.8)	13571	(58.2)	1.11	(1.08-1.13)	1.11 (1.09-1.14)	*<0.001
Malignancy	5231	(42.2)	7166	(57.8)	1.07	(1.04-1.10)		
Chronic renal disease	4624	(42.1)	6350	(57.9)	1.08	(1.06-1.11)		
Cerebrovascular disease	3806	(40.5)	5584	(59.5)	1.12	(1.09-1.15)		
Diabetes mellitus	2701	(42.4)	3676	(57.6)	1.07	(1.03-1.11)	1.04 (1.01-1.07)	*0.009
Cognitive impairment	2725	(46.7)	3109	(53.3)	0.97	(0.94-1.01)		
Liver disease	213	(40.1)	318	(59.9)	1.09	(0.98-1.21)		

* signify a p value of <0.05

¥ Chronic lung disease excluding COPD and asthma

Other cardiac diseases excluding CCF and MI (e.g. hypertension, arrhythmias, valvular heart disease, conduction disorder of the heart, pericarditis, myocarditis)

§ Charlson Comorbidity Index was added to a separate multivariate model with all the listed variables except specific co-morbidities

In a sensitivity analysis excluding previous consulting behaviour in primary care as a factor, multivariate analysis showed a higher probability of consultation in patients aged 50-84 years, length of hospital stay of between 4-7 days, Charlson Comorbidity Index score ≥1 and pre-existing comorbid diseases; COPD, asthma, congestive cardiac failure, myocardial infarction, other cardiac diseases, cancer, chronic renal disease and diabetes mellitus. Lower probability of consultation were seen in 2015/16- 2016/17 (**Table 3-4**). Geographical variation of consultation was again noted, however smoking status was no longer independently associated with consultation.

Table 3-4: Sensitivity analysis excluding primary care consultation in the previous year

	Multivariate CRR sHR (95% CI)		**p value**
Number of patients			
Age			
18-49	1.00	Reference	
50-64	1.14	(1.09-1.18)	*<0.001
65-74	1.15	(1.10-1.20)	*<0.001
75-84	1.10	(1.06-1.15)	*<0.001
≥85	1.01	(0.97-1.05)	0.633
Gender			
Male	1.00	Reference	
Female	1.00	(0.98-1.03)	0.671
CAP admission year			
2002/03-2004/05	1.00	Reference	
2005/06-2006/07	1.08	(1.04-1.13)	*<0.001
2007/08-2008/09	1.03	(0.99-1.08)	0.146
2009/10-2010/11	1.01	(0.97-1.05)	0.788
2011/12-2012/13	1.02	(0.98-1.06)	0.423
2013/14-2014/15	1.02	(0.98-1.06)	0.327
2015/16-2016/17	0.89	(0.84-0.93)	*<0.001
Length of stay			
≤3	1.00	Reference	
4-7	1.04	(1.01-1.07)	0.005
>7	1.00	(0.97-1.03)	0.921
IMD (patient level)			
1 (least deprived)	1.00	Reference	
2	0.96	(0.93-1.00)	0.043
3	0.99	(0.96-1.03)	0.7
4	0.93	(0.90-0.97)	*<0.001

5 (most deprived)	0.92	(0.88-0.95)	*<0.001
Unknown	0.74	(0.49-1.11)	0.143
Practice region			
West Midlands	1.00	Reference	
North West	0.98	(0.94-1.02)	0.247
Yorkshire & The Humber	0.90	(0.84-0.96)	0.001
East Midlands	1.00	(0.93-1.08)	0.963
North East	1.06	(0.99-1.14)	0.106
East of England	1.03	(0.99-1.08)	0.139
South West	0.93	(0.89-0.97)	0.001
South Central	0.90	(0.86-0.94)	*<0.001
London	0.82	(0.78-0.85)	*<0.001
South East Coast	0.81	(0.77-0.84)	*<0.001
§ Charlson Comorbidity Index			
0	1.00	Reference	
1	1.08	(1.04-1.11)	*<0.001
2	1.09	(1.05-1.13)	*<0.001
3	1.17	(1.12-1.21)	*<0.001
4	1.21	(1.16-1.27)	*<0.001
≥5	1.28	(1.23-1.33)	*<0.001
Co-morbidities			
COPD	1.07	(1.04-1.10)	*<0.001
Asthma	1.08	(1.05-1.11)	*<0.001
Chronic lung disease			
Congestive cardiac failure	1.17	(1.13-1.22)	*<0.001
Myocardial infarction	1.14	(1.10-1.19)	*<0.001
Other cardiac diseases	1.16	(1.13-1.19)	*<0.001
Malignancy	1.05	(1.03-1.08)	*<0.001
Chronic renal disease	1.04	(1.01-1.07)	0.013
Cerebrovascular disease			
Diabetes mellitus	1.06	(1.03-1.10)	*<0.001
Cognitive impairment			
Liver disease			

* signify a p value of <0.05

3.3.2 Reasons for consultations and readmissions

The commonest reason for consultation within 30 days was for a respiratory disorder (40.7%) with 11.8% consulting for pneumonia specifically (**Table 3-5**). A small proportion of patients consulted for constitutional symptoms, such as fever, fatigue, loss of appetite or general malaise. Reasons for consultation within 7 days were similar.

Table 3-5: Reasons for GP consultation after hospital discharge

	All patients who consulted		**Patients who consulted before readmission[a]**		**Patients who consulted before death[b]**	
Reason for consultation	**≤ 7 days N= 15,626 n (%)**	**≤30 days N= 31,542 n (%)**	**≤ 7 days N=648 n (%)**	**≤30 days N=3,459 n (%)**	**≤ 7 days N=633 n (%)**	**≤30 days N=2,077 n (%)**
Respiratory	6155 (39.4)	12840 (40.7)	253 (39.0)	1350 (39.0)	158 (25.0)	741 (35.7)
specifically pneumonia	2470 (15.8)	3730 (11.8)	71 (11.0)	293 (8.5)	87 (13.7)	312 (15.0)
Constitutional symptoms	379 (2.4)	1240 (3.9)	16 (2.5)	162 (4.7)	15 (2.4)	84 (4.0)
Digestive	1196 (7.7)	3316 (10.5)	60 (9.3)	439 (12.7)	27 (4.3)	183 (8.8)
Cardiac	1139 (7.3)	2732 (8.7)	50 (7.7)	274 (7.9)	58 (9.2)	209 (10.1)
Genitourinary	466 (3.0)	1629 (5.2)	26 (4.0)	179 (5.2)	16 (2.5)	76 (3.7)
Cognitive	191 (1.2)	558 (1.8)	12 (1.9)	53 (1.5)	16 (2.5)	78 (3.8)

* only Read codes referring to acute symptoms and disorders were included, such as acute cough, acute atrial fibrillation or worsening cognitive impairment; excluding routine reviews for chronic conditions, or routine post-discharge consultations

[a] Readmission within 30 days of discharge

[b] Death within 30 days of discharge

Note: The same patient could fall into multiple categories for 'Reason for consultation'

Of patients readmitted within 30 days of discharge, 38.2% (n=3,459 of 9,051) consulted primary care before readmission. These patients had similar reasons for consulting when compared to all patients. The commonest reason for readmission was pneumonia; 34.6% (n=1,255 of 3,625) and 26.9% (n=2,431 of 9,051) within 7 and 30 days respectively (**Table 3-6**). A large proportion of patients who died within 30 days of discharge consulted primary care before death (60.3%, n=2,077). Of these, 413 of 2077 (19.9%) were for reasons of palliative care or terminal illness (n=230), or cancers (n=183).

Table 3-6: Top 20 reasons for readmission

ICD10	Description	7 days N=3,625 n (%)		30 days N=9,051 n (%)	
J12-J18	Pneumonia	1255	(34.6)	2431	(26.9)
J44	Other chronic obstructive pulmonary disease	194	(5.4)	583	(6.4)
J22	Unspecified acute lower respiratory tract infection	149	(4.1)	400	(4.4)
I50	Heart failure	130	(3.6)	298	(3.3)
N39	Other disorders of urinary system	87	(2.4)	275	(3.0)
R07	Pain in throat and chest	71	(2.0)	224	(2.5)
J69	Pneumonitis due to solids and liquids	58	(1.6)	119	(1.3)
C34	Malignant neoplasm of bronchus and lung	55	(1.5)	170	(1.9)
R06	Abnormalities of breathing	51	(1.4)	142	(1.6)
I26	Pulmonary embolism	47	(1.3)	114	(1.3)
A41	Other sepsis	41	(1.1)	120	(1.3)
J90	Pleural effusion	40	(1.1)	138	(1.5)
K52	Other and unspecified non-infective gastroenteritis and colitis	39	(1.1)	87	(1.0)
I48	Atrial fibrillation and flutter	31	(0.9)	104	(1.1)
I21	Acute myocardial infarction	31	(0.9)	0	(0.0)
R69	Illness, unspecified	29	(0.8)	75	(0.8)
N17	Acute kidney injury	28	(0.8)	80	(0.9)
R41	Other symptoms and signs involving cognitive functions and awareness	27	(0.7)	0	0
K92	Other diseases of digestive system	25	(0.7)	68	(0.8)
R29	Other symptoms and signs involving the nervous and musculoskeletal systems	25	(0.7)	0	0
	Others reasons	1212	(33.4)	3623	(40.0)

3.3.3 Antibiotic prescription at consultation

Antibiotics were prescribed in fewer than 20% of those who consulted within 7 days of discharge compared to 31.1% of those who consulted within 30 days (**Table 3-7**). At consultations within 7 and 30 days of discharge, antibiotics were prescribed for respiratory disorders in 56.4% and 48.9% respectively.

Table 3-7: Antibiotic prescription at consultation

	≤ 7 days n (%)		**≤ 30 days n (%)**	
Frequency of antibiotic courses				
None	12919	(82.7)	21719	(68.9)
One course	2582	(16.5)	7587	(24.0)
Two or more courses	125	(0.8)	2236	(7.1)
Total [#]	15626	(100.0)	31542	(100.0)
Type of antibiotics				
Penicillin	1352	(41.9)	5753	(41.6)
Macrolide	830	(25.7)	3029	(21.9)
Tetracycline	352	(10.9)	1467	(10.6)
Quinolones	220	(6.8)	875	(6.3)
Others	474	(14.7)	2705	(19.6)
Total*	3228	(100.0)	13829	(100.0)

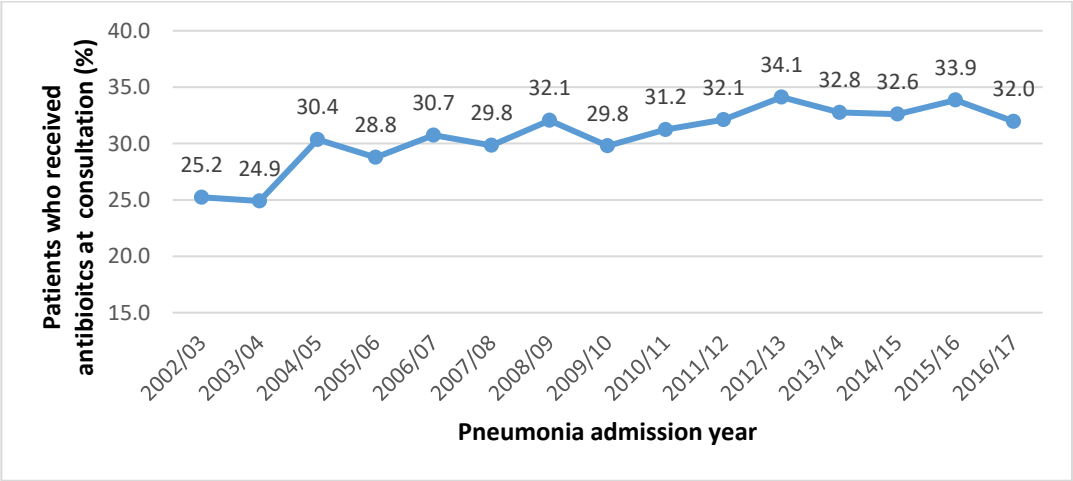
[#] counted by number of people

* counted by number of antibiotic courses

The total for 'Type of antibiotics' do not match one or more courses of antibiotics prescribed due to difference in the way the count was done as listed above.

There was an overall rise of about 9% in antibiotic prescribing from 25.2% in 2002/03 to 34.1% in 2012/13, followed by a declining trend to 32.0% in 2016/17 (**Fig 3-4**). Of those who received antibiotics at consultation, 22.8% received two or more courses of antibiotics within 30 days of discharge. Penicillins and macrolides were the commonest antibiotics prescribed.

Fig 3-4: Trend of antibiotics prescription at primary care consultation over the 15-year study period



Factors independently associated with a higher odds of antibiotic prescription in the first week after discharge were; year of pneumonia hospitalisation and pre-existing COPD or asthma. Factors independently associated with a lower odds of antibiotic prescription were; age ≥65 years, hospital stay ≥4 days, and practice region (East of England and London) (**Table 3-8**).

Table 3-8: Univariate and multivariate logistic regression analyses investigating the important predictors of antibiotic prescription in patients who consulted within the first week of discharge.

Predictors	Univariate LR Crude OR (95% CI)		Multivariate LR Adjusted OR (95% CI)		p value
Age					
18-49	1.00	Reference	1.00	Reference	
50-64	0.86	(0.74-1.00)	0.90	(0.78-1.05)	0.169
65-74	0.78	(0.68-0.90)	0.81	(0.70-0.94)	*0.005
75-84	0.76	(0.67-0.87)	0.82	(0.72-0.95)	*0.007
≥85	0.73	(0.64-0.84)	0.84	(0.73-0.98)	*0.023
Gender					
Male	1.00	Reference	1.00	Reference	
Female	1.07	(0.98-1.16)	1.08	(0.99-1.17)	0.092
CAP admission year					
2002/03-2004/05	1.00	Reference	1.00	Reference	
2005/06-2006/07	1.19	(1.00-1.41)	1.16	(0.97-1.37)	0.098
2007/08-2008/09	1.40	(1.19-1.65)	1.36	(1.16-1.60)	*<0.001

2009/10-2010/11	1.19	(1.02-1.40)	1.17	(1.00-1.37)	0.057
2011/12-2012/13	1.26	(1.08-1.47)	1.25	(1.07-1.46)	*0.005
2013/14-2014/15	1.29	(1.10-1.51)	1.27	(1.08-1.49)	*0.003
2015/16-2016/17	1.23	(1.03-1.48)	1.21	(1.00-1.45)	*0.047
Length of stay					
≤3	1.00	Reference	1.00	Reference	
4-7	0.74	(0.67-0.82)	0.75	(0.67-0.84)	*<0.001
>7	0.63	(0.57-0.69)	0.65	(0.59-0.72)	*<0.001
Practice region					
West Midlands	1.00	Reference	1.00	Reference	
North West	0.97	(0.84-1.12)	0.94	(0.82-1.09)	0.435
Yorkshire & The Humber	0.96	(0.75-1.24)	0.98	(0.76-1.27)	0.892
East Midlands	0.91	(0.69-1.21)	0.93	(0.70-1.24)	0.616
North East	0.86	(0.66-1.13)	0.85	(0.65-1.12)	0.252
East of England	0.82	(0.70-0.97)	0.83	(0.70-0.98)	*0.03
South West	0.88	(0.76-1.04)	0.90	(0.77-1.05)	0.181
South Central	0.99	(0.84-1.16)	0.98	(0.84-1.16)	0.853
London	0.68	(0.57-0.81)	0.67	(0.56-0.80)	*<0.001
South East Coast	0.91	(0.78-1.08)	0.91	(0.77-1.07)	0.257
Co-morbidities					
COPD	1.14	(1.04-1.26)	1.13	(1.01-1.26)	*0.036
Asthma	1.31	(1.19-1.44)	1.25	(1.13-1.38)	*<0.001
[¥]Chronic lung disease	1.18	(0.85-1.62)			
Congestive cardiac failure	0.98	(0.86-1.12)			
Myocardial infarction	0.88	(0.77-1.02)			
#Other cardiac diseases	0.88	(0.81-0.95)			
Malignancy	0.89	(0.81-0.99)			
Chronic renal disease	0.96	(0.87-1.07)			
Cerebrovascular disease	0.94	(0.83-1.07)			
Diabetes mellitus	0.95	(0.85-1.06)			
Cognitive impairment	1.09	(0.95-1.24)			
Liver disease	0.80	(0.51-1.26)			

[*] signify a p value of <0.05

In addition to the variables listed in the table, univariate logistic regression showed no association between antibiotic prescription at consultation and smoking status, alcohol consumption, IMD score, primary care consultation in the previous year and Charlson Comorbidity Index.

[¥] Chronic lung disease excluding COPD and asthma

[#] Other cardiac diseases excluding CCF and MI (e.g. hypertension, arrhythmias, valvular heart disease, conduction disorder of the heart, pericarditis, myocarditis)

3.4 Discussion

3.4.1 Principal findings

To our knowledge, this is the first study to describe the impact on primary care following discharge of adults hospitalised for pneumonia across England. We found a previously unrecognised large burden of care with almost 56% of patients consulting primary care within 30 days of hospital discharge, the highest rate of consultation occurring within 7 days. Nearly 40% of consultations were for a respiratory disorder, with 12% consulting for pneumonia specifically and 30% of patients consulting received further antibiotics. Previous consultation behaviour at primary care was the strongest predictor of consultation.

3.4.2 Strengths & Weakness of the study

A major strength of this study is the large, nationally representative study cohort of over 56,000 patients obtained through linkage between the CPRD and HES, two large validated medical record databases.[58] This dataset reflects the real-world practice of pneumonia in NHS England covering a span of 15 years. In order to avoid measuring non-medically relevant consultation and ensure face-to-face consultations were captured, administration-related Read codes were judiciously excluded. Compared to relying on CPRD coding alone, the HES-CPRD linkage enabled patients hospitalised with pneumonia to be more accurately identified and allowed confident exclusion of patients with hospital acquired pneumonia. The 15-year study period also enabled an examination of time-trends in relation to the outcomes of interest.

A weakness of this study is that although CPRD contains data from all of the UK, these data are predominantly from England and linked datasets including HES are only available

for English practices. Therefore, the results from this study may not be generalisable to the rest of the UK. Secondly, a large number of patients (n=87,773) were excluded because their data did not meet the minimum research quality checks or their first practice registration date to date of admission was less than a year. These patients were younger than those included (median 71 vs 75 years, p<0.0001) and there was a higher proportion of females (51.5% vs 50.4%). Those discharged to a care facility outside the catchment area of their previous primary care practice would also have been excluded from the analysis. Excluded patients may have different patterns of consultation behaviour compared to the study cohort. Thirdly, we relied on ICD-10 coding for the identification of patients with pneumonia. Information bias from possible miscategorisation of pneumonia is a recognised limitation of reliance on HES coding. Roughly a third of ICD-10 coded cases of pneumonia within HES lack radiographic evidence of pneumonia and would strictly be considered cases of non-pneumonic LRTI.[30] The vast majority of these patients are nevertheless treated clinically as having pneumonia and inclusion of these patients in the analysis reflects real-world practice. Fourthly, although considerable efforts were made to ensure data quality, we cannot fully exclude the possibility of miscategorisation of outcomes arising from miscoding consultations after discharge.

3.4.3 Comparison with other studies

Very few studies have examined the impact on primary care following hospital discharge for an episode of pneumonia. A Dutch study using electronic health records observed that after hospitalisation for CAP, only 8% of adults consulted primary care within 30 days.[85] Their study comprised patients a) who were younger (mean age range per year from 2002- 2009; 57 years (SD 27.9) to 61 years (SD 24.8), compared to a median age of 76 years (IQR 60-85) for our study cohort and b) with lower pneumonia severity, as

reflected in their combined mortality (in-hospital and within 30 days of discharge) of 7%, compared to 26.7% in our study. Differences in healthcare systems and help-seeking behaviour may also have contributed. Two Spanish studies (a prospective cohort study at a tertiary hospital (n=934) and a multicentre clinical trial (n=207)) observed consultation proportions of 18-20%.[86,87] A small 3-centre UK study by Daniel *et al.* (n=108) of adults aged <65 years found primary care consultation occurred in 59%.[47]

We found a lower proportion of consultation due to respiratory symptoms compared to Daniel *et al.* and Adamuz *et al. (*69% and 75% respectively). Direct comparison between these studies is not possible due to the use of different methodologies for measuring and categorising reasons for consultation.[47,87] Antibiotic use at consultation in our study (30.8%) was similar to that reported by Daniel *et al.* (34.4%).[47]

Other studies have investigated the burden of reconsultations after initial management at primary care of patients with lower respiratory tract infections (RTIs) or acute bronchitis.[49,88–90] The patient cohorts in these primary care studies are mostly different, often involving adults with self-limiting RTIs in whom the challenge is the avoidance of overuse of antibiotics and managing patient expectation. In these patient groups, reconsultations were observed in 20 - 33%. Similar to other research in lower RTI consultations not requiring hospital admission, we found that a prior history of consultation was a strong predictor of further consultation.[48,49] Strategies such as the provision of patient information leaflets, or delayed prescriptions, for previously well adults presenting with RTIs have been tested and found to reduce reconsultation rate.[48,91,92] Such strategies may be relevant in managing patients' expectations on discharge from hospital as well. In addition, existing integrated care pathways between primary and secondary care for the post-discharge management of patients may provide

applicable approaches to improving the quality of care and patients' experiences following pneumonia.[93,94]

Patients with a shorter length of hospital stay might be expected to have a reduced likelihood of further antibiotic prescription at consultation. We observed the opposite effect. In those who consulted primary care, patients with shorter hospital stays (<4 days) were more likely to receive antibiotics compared to those with longer hospital stays. Further studies are required to determine the reasons for antibiotic prescription at these consultations and their appropriateness.

3.4.4 Possible explanations & implications for clinicians & policymakers

Consultation following hospitalisation for pneumonia may serve as a means of safety-netting, providing an opportunity for clinicians to identify deteriorating patients who need further medical intervention or sometimes readmission. However, patients often continue to report persistence of symptoms, including fatigue, cough and dyspnoea, associated with functional impairment for several weeks after discharge from hospital.[54] Results from two qualitative studies in this group of patients reveal that at the time of hospital discharge, patients lack a clear understanding about the short and long-term consequences of CAP, or the natural course of their symptoms.[95,96] Many patients describe a sense of isolation when their experiences of relatively slow recovery do not match the expectations of relatives, carers and even physicians.[95,96] Such ongoing unaddressed patient needs may contribute towards the high level of consultation observed as patients seek reassurance of adequate recovery.

At a strategic level, lack of recognition of the burden of morbidity during recovery from pneumonia has thus far meant that evidence-based interventions to meet patients' needs have not been adequately developed. The health economic costs of primary care consultations are considerable. Annually, over 100,000 patients are admitted to hospital in England with CAP.[97] Assuming a cost of £30 for each primary care consultation, we estimate post-pneumonia consultations alone to cost the NHS approximately £2 million a year.[98] These figures do not take into account any additional NHS and ecological costs from antibiotic prescribing nor the impacts from 'long-COVID' consequent on SARS-CoV2 infection specifically.[99–102]

Education of patients, the public, clinicians and policy makers regarding the sometimes prolonged morbidity associated with hospitalisation with pneumonia is important to create the understanding and space necessary to support patient recovery. One clinical trial demonstrated that having a dedicated nurse provide individualised patient education over two sessions between 24-72 hours before discharge reduced consultations in primary care and hospital readmissions.[86]

The observation that previous consultation behaviour is strongly associated with post-pneumonia discharge consultation raises the question of whether the index pneumonia admission is a precipitating event leading to further health consequences, or whether it is only a marker of on-going health needs. It is likely that both these explanations play some part. Further studies are required to better understand the relative contributions of these factors and to inform where to direct health improvement efforts.

A significant trend toward lower levels of post-discharge consultations was observed over the 15 years of the study (2002 to 2017). Over that period, concerted efforts were made

nationally to improve the care of patients with CAP including major updates of national CAP Guidelines (from the British Thoracic Society in 2009, and NICE in 2014).[2,3] A corresponding decrease in mortality from CAP over a ten-year period (2009 to 2019) was also observed.[30] These initiatives may have contributed to the observed decrease in post-discharge consultations and supports continued efforts in this direction through the NHS Long Term Plan focus on pneumonia.

Chapter 4

Chapter 4 Cardiac complications following community-acquired pneumonia: A systematic review and meta-analysis

4.1 Introduction

Community-acquired pneumonia (CAP) and cardiac disease are the leading causes of morbidity and mortality worldwide. Twenty-five studies from the past decade alone have shown that there is a strong link between CAP and cardiac complications including acute coronary syndrome (ACS), heart failure and arrhythmias. Patients hospitalised with CAP have substantial mortality ranging from 5.1% to 47% depending on the age, severity, pneumonia aetiology and co-morbidities.[29,97,103] The additional burden of cardiac complications will undoubtedly worsen their prognosis, highlighting the need to focus on this important global issue.

Cardiovascular disease is a broad terminology that covers a group of disorders of the heart and blood vessels including hypertension, coronary heart disease, heart failure, cerebrovascular disease, vascular dementia and peripheral vascular disease.[104,105] In contrast, cardiac disease refers to disorders specifically related to the heart. To date, three reviews have covered CAP and cardiac or cardiovascular complications. The first meta-analysis by Fine et al. in 1996 reported a pooled incidence rate of 8.6% (95% CI 6.4-12.3) for heart failure (n=4 studies) following CAP.[106] Corrales-Medina et al. in 2011 included 25 studies in their systematic review. Although the objective of their study was to examine cardiac complications, studies with cardiovascular complications were also included.[107] The pooled incidence rates of ACS, heart failure and arrhythmias within 30 days of CAP diagnosis (either as inpatient or outpatient) were 5.3%, 14.1% and 4.7% respectively. Likewise, an updated systematic review by Tralhao et al. also included cardiovascular studies from both inpatient and outpatient settings, however a key point was not taken into account during analysis. No distinction was made between the included studies for the time at which the outcome i.e. cardiac or cardiovascular complication was measured.[108]

The aim of this systematic review was to focus on the incident cardiac complications following hospitalisation for community-acquired pneumonia (CAP), with particular attention to the temporal relationship of these complications in relation to CAP, which may affect development of management strategies. We have also summarised the available evidence regarding the mortality, risk factors as well as biomarkers associated with developing these incident cardiac complications.

4.2 Methods

This systematic review was conducted using a predefined protocol which was registered with PROSPERO database (CRD42019123996, Appendix 3) and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.

4.2.1 Search strategy and study selection

The search strategy which was designed to find published studies included subject headings and keywords related to CAP and cardiac complications such as acute coronary syndromes, heart failure and arrhythmias. Comprehensive searches of MEDLINE and Embase from inception to December 2018 were conducted. Details of the search strategy are found in Appendix 4. The reference list of all included studies and previously published relevant reviews were screened for inclusion.

This review included observational studies. Studies published in all languages were considered and no date restrictions were placed on searches. Studies comprising adults aged 18 years and above with a clinical and radiological diagnosis of CAP were included. Studies comprising patients with hospital-acquired pneumonia, aspiration pneumonia,

active pulmonary tuberculosis (TB) and post-obstructive pneumonia secondary to thoracic malignancy were excluded.

Two reviewers (VB and TM) independently screened titles and abstracts using Rayyan software[109] and subsequently reviewed full-texts of retrieved studies for eligibility. Disagreement was resolved by discussion and consensus, involving a third reviewer where necessary.

4.2.2 Data extraction and assessment of methodological quality

Two reviewers (VB, HL, DA, SQ or TM) independently extracted data for all studies using a standardised form created for this study (Appendix 5). Any disagreements that arose between reviewers were resolved through discussion, or with a third reviewer (TM) when required. The following information were collected: study population, study design, exposure of interest (CAP) and outcomes including i) incidence of cardiac complications (i.e. acute coronary syndrome including myocardial infarction (MI) and unstable angina, new or worsening heart failure and new or worsening arrhythmia), ii) mortality associated with cardiac complications, iii) risk factors for developing cardiac complications, and iv) biomarkers which are associated with cardiac complications. Methodological quality and risk of bias was assessed using the modified Newcastle-Ottawa Quality Assessment Scale (Appendix 5) for either cohort or case-control studies depending on individual study design. This scale is based on three broad categories; (1) selection of the study sample, (2) comparability of the sample groups (for studies that adjust for confounders, age was *a priori* confounder) and (3) ascertainment of exposure and outcome. Thus, studies were scored out of either a total of five, seven or nine points depending on the study type. Scores were chosen *a priori* to indicate different levels of methodological quality; high quality studies had a score of either ≥4/5, ≥5/7 or ≥6/9.

4.2.3 Data synthesis & Statistical analysis

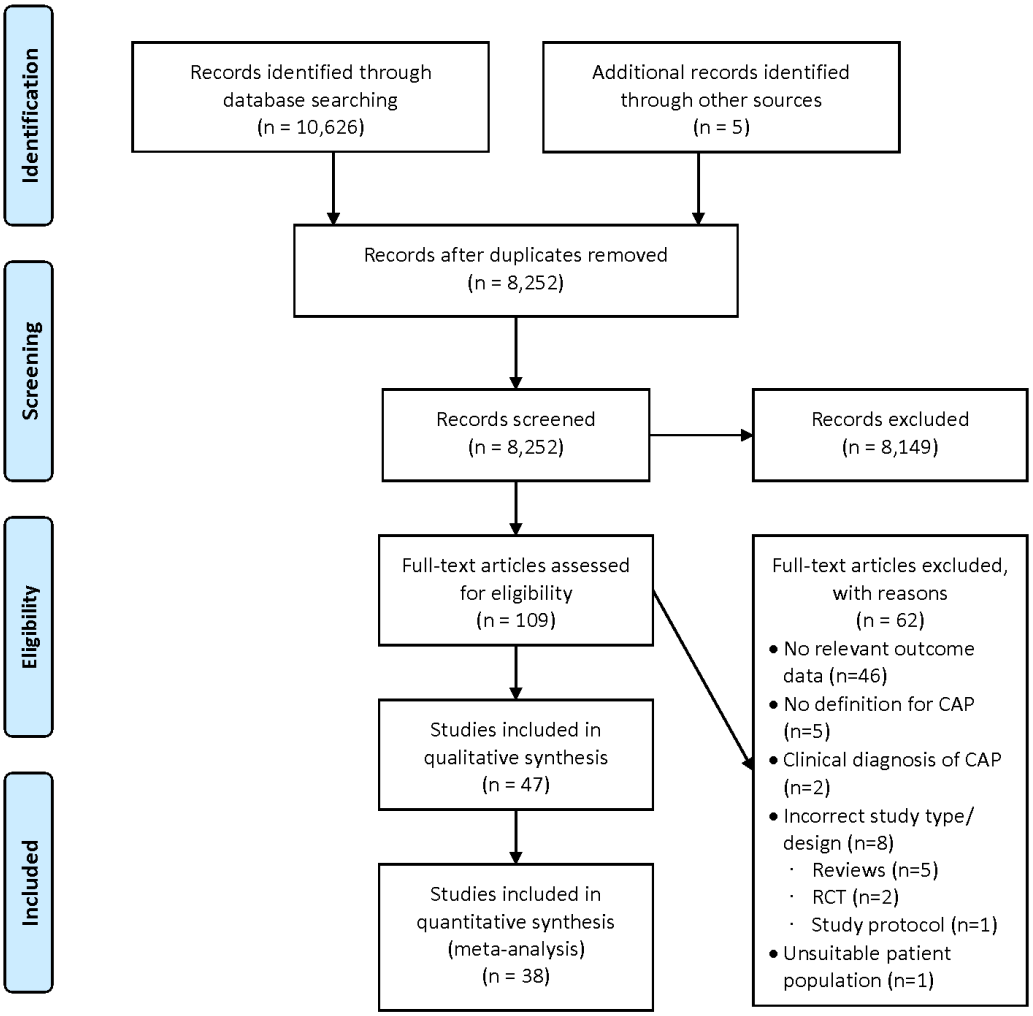
Where possible, the pooled incidence of ACS, heart failure and arrhythmia were determined using a random effects model (DerSimonian Laird weights methods), stabilising the variances using the Freeman-Tukey double arcsine transformation so that studies with proportions close to 0% or 100% were approximately estimated, with computation of exact binomial 95% confidence intervals at different time-points (e.g. on admission, in-hospital, 30 days, 90 days and 1 year).[110] Studies with pooled ORs for the risk factors of developing incident cardiac complications and associated mortality were summarised with 95% confidence intervals. Measures of effect adjusted for confounders (age was an *a priori* confounder) were used in preference to crude measures of effect. One study reported MI and unstable angina separately, hence they were included separately.[111] The I^2 statistic was used to assist with assessment of heterogeneity between studies. As we anticipated a high level of heterogeneity for the pooled incidence of incident cardiac complications, an *a priori* decision was made not to abandon the meta-analyses due to high heterogeneity.

Publication bias was not assessed in this review as the utility of standard publication bias tests for proportional meta-analyses has been questioned, with funnel plots and statistical tests potentially yielding misleading and inaccurate results.[112] Although publication bias may cause inflated estimates in meta-analyses of studies of treatment effect, this is unlikely in the context of studies reporting the proportion of patients with cardiac complications after CAP. All analyses were conducted using StataMP/ 15.1.

4.3 Results

Out of 10,631 studies identified, 109 full-text articles (including five non-English studies; one Spanish, one Russian, one Hungarian and two Chinese studies) were reviewed (**Fig 4-1**). Forty-seven English studies with 134,966 participants were included in the systematic review from 1984- 2019 (**Table 4-1**). The most common reason for exclusion was lack of documented relevant outcome data (n= 46/63).

Fig 4-1: PRISMA flow diagram for study selection



4.3.1 Characteristics on included studies

Of 47 included studies for the systematic review, there were 43 cohort studies, one case-control study and three case series. All studies included both genders, however the study population for five studies were predominantly male (98%). The definition of CAP was based on radiological confirmation in 42 studies and diagnostic coding (International Classification of Diseases, ICD coding) in five studies. All studies included patients who were admitted to hospital for CAP and five studies included patients admitted to the intensive care unit (ICU).

Table 4-1: Characteristics of 47 included studies for systematic review; ordered by year.

First Author	Publication year	Study design	Country	Study period	Inclusion criteria	Exclusion criteria	N	Outcome of interest			
								Overall	Heart failure	Arrhythmia	ACS
Esposito[113]	1984	Single-centre prospective cohort	US	Dec 1980-April 1983	Adults ≥65 years Mean age: 61 Male: 39.5% Follow-up: Hospitalisation, LOS 15.7 days	Admitted for terminal care	38		✓		
Allen[114]	1984	Single-centre prospective cohort	Africa	July 1981-Jan 1983	Adults Mean age: 39 Male: 72.1% Follow-up: Hospitalisation	• Refused inpatient treatment • pulmonary TB • lung abscess • empyema • bronchitis	502			✓	
Marrie[115]	1989	Single-centre prospective cohort	Canada	Nov 1981-March 1987	Adults Mean age: 63.2 Male: 61.3% Follow-up: Hospitalisation, mean LOS 17.4 days	• HAP • patients with other causes for their pulmonary opacity (e.g. CCF or pulmonary infarction)	719		✓		
Fine[116]	1990	Single-centre prospective cohort	US	Jan 1988-Nov 1988	Adults> 18 Mean age: 57.5 (21) Male: 57% Follow-up: 6 weeks	• HAP • a prior episode of pneumonia within 6 weeks of presentation • radiographic abnormalities attributed solely to CCF, carcinoma or pulmonary embolus • known positive test for antibodies to HIV or a clinical diagnosis of AIDS • nursing home/ chronic care facility residents	280		✓		✓

Venkatesan[117]	1990	Single-centre prospective cohort	UK	Nov 1987-May 1988	Adults aged ≥65 Median age: 79 (range 65-97) Male: 52% Follow-up: 6 weeks	• pneumonia as a terminal event	73		✓	
Leroy[118]	1992	Single-centre retrospective cohort	France	Jan 1987-Dec 1991	Adults >16 Mean age: 63.9 (17.6) Male: 63% Follow-up: ICU stay	• HAP • AIDS • radiographic abnormalities solely attributed to either carcinoma, CCF, pulmonary embolus, or chronic lung disease	299	Acute coronary or ventricular insufficiency		
Woodhead[119]	1992	Multicentre retrospective cohort	UK	Jan- Dec 1987	Adults >15 years admitted to ICU Mean age: 54 Male: 57% Follow-up: Mean 669 days (range 473-866)	• immunosuppressed • CAP secondary to bronchial obstruction by foreign body or malignancy	60		✓	✓
Musher[120]	2000	Single-centre prospective cohort	US	Sept 1996-March 1997, Sept 1997-April 1999	Adults with pneumococcal pneumonia Mean age: 61.5 (range 38-91) Male: 98% Follow-up: 90 days	• microscopic examination of the Gram-stained sputum failed to show a clear predominance of forms typical for pneumococcus in areas that contained ≥20 WBC per epithelial cell • culture of the sputum revealed other potential infecting organism(s) • lack clinical or laboratory findings suggestive of an acute bacterial pneumonia • blood cultures were negative, but they had not been obtained before the first dose of antibiotics	100		✓	✓

Fernande-Sabe[121]	2003	Single-centre prospective cohort	Spain	Feb 1995-July 2001	Adults ≥16 years Mean age: 65.2 Male: 69.9% Follow-up: 30 days	• severely immunosuppressed • nursing home residents	1,474		✓	
Martinez-Moragon[122]	2004	Single-centre prospective cohort	Spain	Jan 2003-July 2003	Adults >65 years Mean age: 75.5 (6.2) Male: 44% Follow-up: Hospitalisation, mean LOS 8.4 days (SD 5.9)	• HAP • CAP was not the main cause of hospitalization	91	✓		
Menendez[123]	2004	Multicentre prospective cohort	Spain	Oct 2000-April 2001	Adults>16 Mean age: 68 (range 16-98) Male: 66.9% Follow-up: 30 days	• HAP • immunosuppressed • leukopenia/ neutropenia unless attributable to pneumonia • died within the first 48 hours after admission	1,424	✓		
Querol-Ribelles[124]	2004	Single-centre prospective cohort	Spain	Jan 2000 – Sept 2003	Adults >18 years Mean age: 70.5 Male: 70.8% Follow-up: 30 days	• HAP • neutropenia due to chemotherapy • haematological neoplasms • direct admission from ED to the ICU	459		✓	
Diaz[125]	2005	Single-centre prospective case series	Chile	July 1999-June 2001	Adults (>15 years) admitted to ITU during the first 24 hours after admission Mean age: 73 (15) Male: 58.4 Follow-up: 30 days	• immunosuppressed • solid or hematologic tumours in chemotherapy • neutropenia (white blood cell count <1,000 / mm^3) • pneumonia as a terminal event	113		✓	✓

Marrie[126]	2005	Multicentre prospective cohort	Canada	Nov 2000-Nov 2002	Adults with CAP Mean age: 43.6 (14.8) Male: 48.8 Follow-up: Hospitalisation, mean LOS 7.4 days (SD 11.1)	• direct admission from ED to the ICU • aspiration pneumonia, but were included in second year • TB • cystic fibrosis • pregnant and nursing mothers • immunosuppressed	3,065	✓	✓
O'Meara *[127]	2005	Multicentre prospective cohort	US	1989-2001	Adults ≥65 years Mean age: 75 Male: 49% Follow-up: 10.7 years	• institutionalised • not ambulatory at home • under hospice care • receiving radiation or chemotherapy for cancer • not expected to remain in the area for ≥ 3 years • unable to be interviewed.	582		✓
Becker *[128]	2007	Multicentre retrospective case-series	Canada	Jan 2003-May 2004	Adults >45 Mean age: 76.6 (12.2) Male: 50.4% Follow-up: Hospitalisation	• lack of evidence on chest radiograph of pneumonia • lack of serum glucose measurement within 24 h of admission active cancer • pulmonary TB • AIDS	391	✓	✓	✓
Musher[129]	2007	Retrospective case series	US	Jan 2001-Dec 2005	Adults with pneumococcal pneumonia Follow-up: Hospitalisation	• terminal arrhythmias	170	✓	✓	✓
Aliberti[130]	2008	Single-centre retrospective cohort	US	June 2001-March 2006	Adults ≥18 years Mean age: 69.4 (12.3) Male: 97.8% Follow-up: 28 days	-	500	✓	✓	✓

Cabre[131]	2008	Single-centre prospective cohort	Spain	Jan 2001-Aug 2005	Adults >70 Mean age: 84.7 (6.5) Male: 59% Follow-up: Until death or ≥30 days	• HAP • immunosuppressed • pneumonia as a terminal event	117	✓	✓	✓
Ramirez[132]	2008	Single-centre prospective cohort	US	June 2001-March 2006	Elderly adults in ICU Mean age: 69.3 (12.4) Male: 98% Follow-up: 30 days	• patients with elevated troponin levels and a concomitant diagnosis of severe sepsis were excluded from the group of patients with AMI	500			✓
Corrales-Medina[133]	2009	Retrospective single-centre cohort	US	Jan 2000-Dec 2006	Adults Mean age: 68 (12.8) Follow-up: 15 days	• immunosuppressed • excluded as controls if their reason for hospital admission was an elective or therapeutic procedure, or their diagnosis of admission was either pneumonia or ACS.	601			✓
Mandal *[134]	2011	Multicentre retrospective cohort	Scotland	2005-2007	Adults ≥18 years Median age: 73 (IQR 52-82) Male: 48% Follow-up: 90 days	• HAP • admission or transfer from a health-care facility • post-operative pneumonia • HIV	4408		✓	✓
Perry *[111]	2011	Multicentre retrospective cohort	US	Oct 2001-Sept 2007	• ≥65 yrs old • ≥ 1 year of VA outpatient care before admission; were hospitalized for at least 24 hours; and had received at least 1 dose of antibiotics within 48 hours of admission. Mean age: 77.5 (6.7) Male: 98% Follow-up: 90 days	-	50,119	✓	✓	✓

Morlacchi[135]	2011	Multicentre prospective cohort	Italy, Switzerland, US	Oct 2009 – Dec 2010	Adults ≥18 years with CAP & HCAP Mean age: 73 (16) Male: 56% Follow-up: 30 days	• HAP • unstable psychiatric or psychological condition rendering the subject unlikely to be cooperative or to complete the study requirements.	431	✓	✓	✓
Corrales-Medina[136]	2012	Multicentre prospective cohort	US, Canada	Oct 1991 – March 1994	Adults ≥18 years Mean age: 56.2 (10.8) Male: 50% Follow-up: 30 days	• HAP • radiographic findings were considered to represent a pre-existing infiltrate or if they were consistent with an alternative diagnosis (e.g. lung carcinoma, pulmonary oedema or pulmonary embolus) • HIV infection • previous enrolment in the study	2,287	✓	✓	✓
Griffin[137]	2013	Multicentre retrospective cohort	13 countries	June 2011 – Nov 2012	Adults ≥ 16 years Median age: Cardiac events 78 (IQR 21), Without cardiac events 64 (IQR 33) Male: 58% Follow-up: 28 days	• HAP	3,068	✓	✓	✓
Viasus[138]	2013	Single-centre prospective cohort	Spain	Feb 1995-Dec 2010	Mean age: 66.3 (17) Male: 68% Follow-up: 30 days	-	3,921	✓	✓	✓

Cangemi[139]	2014	Multicentre prospective cohort	Italy	Oct 2011 – April 2013	Adults ≥18 years Mean age: 70 (15.7) Male: 60.3% Follow-up: Hospitalisation, mean LOS 10 days	• HCAP • radiographic evidence of pre-existing infiltrates • severe sepsis • immunosuppression • presence of malignancy • pregnancy or breastfeeding • allergy to antibiotics	278			✓
Corrales-Medina[140]	2014	Multicentre prospective cohort (validation cohort)	US, Canada	Feb 1998 - March 1999	Age ≥18 years Mean age: 68.5 (17.1) Male: 46% Follow-up: 30 days	• HAP • cystic fibrosis, active pulmonary TB, immunosuppression or HIV infection • current illicit drug use or alcohol abuse with documented end-organ damage • palliative care only • homelessness • hospital stay less than 2 days • a culture positive for methicillin-resistant S. aureus infection within 24 hours of presentation or current treatment for this infection • unresolved or incompletely treated pneumonia or empyema diagnosed within the 30 days preceding presentation • previous enrolment in the study	608	✓	✓	✓
Dutt[141]	2014	Single-centre retrospective cohort	India	Jan 2011-Jan 2012	Adults with ACE after 48-72 hours of hospital stay Mean age: 53 (range 30-75) Male: 61.9% Follow-up: 72 hours	• HAP • severe sepsis with a concomitant elevated troponin level	105			

Tang * [142]	2014	Multicentre retrospective cohort	US	Oct 2001-Sept 2007	Adults ≥ 65 years with ≥ 1 Veteran Affairs (VA) outpatient clinic visit in the preceding year and ≥ 1 active and filled outpatient medication from a VA pharmacy within 90 days of admission Mean age: 77 (6.5) Male: 98% Follow-up: 30 days	• patients who died during the initial hospitalisation • admitted to hospitals with <25 reported hospitalisations during study period	45,134		✓	✓	✓
Aliberti [143]	2015	Multicentre prospective cohort	Italy, Switzerland	Oct 2009-Oct 2012	Adults (⩾18 years) with CAP and healthcare-associated pneumonia Median age (AMI): 79 (IQR 72-85) Male: 58.3% Follow-up: 30 days	• HAP	905		✓	✓	✓
Bello [144]	2015	Single-centre prospective cohort	Spain	Apr 2008-Nov 2011	Adults (>18 years) with CAP within 24 hours of arrival. Mean age: 69 (15) Male: 63% Follow-up: 1018 days (SD 539)	• HAP • immunosuppression • leukopenia/ neutropenia/ and/or chemotherapy in the previous year • pulmonary abscess (radiological cavitation), aspiration pneumonia and obstructive pneumonia; • presence of malignancy	265	✓			

Cangemi[145]	2015	Single-centre prospective cohort	Italy	Jan 2011-Dec 2014	Adults ≥18 years Mean age: 71.8 (15.7) Male: 62.1% Follow-up: Median 17.4 months	• HAP & HCAP • radiographic evidence of a pre-existing infiltrates • immunosuppression • presence of malignancy • pregnancy or breast feeding • allergy to antibiotics • refusal to sign informed consent	301		✓	✓
Chen[146]	2015	Single-centre retrospective cohort	Taiwan	June 2007-Aug 2012	Adults Mean age: 77.5 (11.3) Male: 63.5% Follow-up: Hospitalisation	• HAP • patients with concurrent infections • use of steroids • hypoglycaemia	203			✓
Shebl[147]	2015	Single prospective cohort	Egypt	July 2012-Sept 2014	Adults Mean age: 59 (19.3) Male: 52.3% Follow-up: Hospitalisation; mean LOS 12.2 days (7.6)	• presence of an alternative diagnosis that likely explained the pulmonary symptoms and X-ray infiltrate (e.g. lung carcinoma, pulmonary oedema, or pulmonary embolus)	130	✓	✓	✓
Vannuchi[148]	2015	Prospective single-centre cohort	Italy	Jan 2013-July 2014	Elderly patients with CAP Follow-up: 30 days	-	165	✓		
Violi[149]	2015	Multicentre prospective cohort	Italy	Oct 2011 – June 2014	Adults ≥18 years Mean age: 70.5 (15.5) Male: 62.5% Follow-up: Hospitalisation, mean LOS 10 days	• HAP • pre-existing permanent or persistent AF • severe sepsis • immunosuppression • presence of malignancy • pregnancy or breast feeding	432		✓	

Aliberti[150]	2016	Multicentre prospective case-control	Italy	Sept 2011-Jan 2013	Adults with CAP & HCAP Median age: 75 (cases)/ 68 (controls) Male: 57.4% Follow-up: Hospitalisation, median LOS 9 days (7-14)	• HAP • absence of sinus rhythm on ECG at hospital admission • pacemaker rhythm on ECG at hospital admission • undergoing mechanical ventilation • on chronic treatment with inhaled long acting either muscarinic agents or beta agonists.	101		✓	✓	✓
Zhang[151]	2016	Single-centre retrospective cohort + Self-controlled case series	China	Jan 2012-Dec 2014	Adults ≥18 years Mean age: 57.9 (17.5) Male: 48.6% Follow-up: • Cohort: Mean 12.8 months • Self-controlled case analysis: 745 days	• TB • the presence of an alternative diagnosis that likely explained the pulmonary symptoms and X-ray infiltrate (e.g. lung cancer, non-infectious interstitial lung diseases, pulmonary oedema, atelectasis, pulmonary embolism, pulmonary eosinophil infiltration and pulmonary vasculitis) • CCF, with liver or renal function failure • ACS • acute cerebrovascular events.	372	Heart failure and ACS			

Eurich[152]	2017	Multicentre prospective cohort	Canada	2000 - 2002	Adults >17 years Mean age: 55 (20) Male: 53.1% Follow-up: Median 9.9 years (IQR 5.9-10.6)	• TB • cystic fibrosis • immunocompromised • pregnant.	4,988	✓		
Violi[153]	2017	Prospective multi-centre cohort	Canada	Oct 2011-Jan 2016	Adults ≥18 years Mean age: 73.1 (14.1) Male: 41% Follow-up: 30 days	• HAP • radiographic evidence of pre-existing infiltrates • immunosuppression • presence of malignancy • pregnancy or breastfeeding • severe allergy to antibiotics	1,182	✓	✓	✓
Frencken[154]	2017	Multicentre prospective cohort	Netherlands	Jan 2011-May 2015	Adults admitted to ICU Mean age: 63.9 Male: 63.1% Follow-up: 30 days	• HAP • cardiopulmonary resuscitation before ICU admission • not meeting criteria for organ failure • transferred from other hospitals.	179			✓

Cilli[155]	2018	Multicentre retrospective cohort	Turkey	Jan 2009-Dec 2015	Adults admitted to ICU Mean age: 68 (16) Male: 61.4% Follow-up: ICU stay	• HAP • immunosuppression • presence of malignancy • the presence of an alternative diagnosis that likely explained the pulmonary symptoms and x-ray infiltrate (e.g. lung carcinoma, pulmonary oedema, or pulmonary embolus)	373	✓	✓	✓
Cangemi[156]	2019	Single-centre prospective cohort	Italy	Oct 2011-Oct 2018	Adults ≥18 years Mean age: 70.4 (16.8) Male: 62.9% Follow-up: Hospitalisation, median LOS 11 days (IQR 9-15)	• pre-existing permanent or persistent AF • severe sepsis • immunosuppression • presence of malignancy • pregnancy, or breastfeeding.	472		✓	
Pieralli[157]	2019	Multicentre prospective cohort	Italy	Nov 2013-July 2016	Adults ≥18 years, sinus rhythm confirmed by ECG on admission, no previous documented episodes of AF Mean age: 75.5 (14.4) Male: 48% Follow-up: Hospitalisation, mean LOS 9.5 (SD 5.1)	• HAP • immunocompromised • refused/ unable to give their consent.	468		✓	

4.3.2 Risk of bias

Based on the chosen *a priori* scores, 33 studies were of high-quality and 14 studies were of low to moderate quality (**Table 4-2**). In the risk of bias assessment for study selection domain, 20 of 47 studies (42.3%) were judged to have an element of selection bias; 17 studies had patients who may not have been truly representative of patients with CAP and cardiac complications due to a combination of selected group of certain age, predominantly male population and from ICU cohort, and in eight studies, there was no explicit statement that the cardiac complication was not present at the start of the study. For studies that adjust for confounders, in the comparability of the sample groups domain, three of 18 studies (16.7%) did not control for the *a priori* confounder, age. As for the ascertainment of outcome domain, 20 of 47 studies (42.6%) were at some risk of bias, generally attributable to lack of description of the assessment of confirmation of the cardiac complications (n=18 studies). In the remaining two studies, one did not describe the non-response rate and one did not have statement for adequacy of follow-up.

Table 4-2: Risk of bias for included studies (using Newcastle Ottawa Scale)

Cohort studies, maximum score= 5

First Author	Publication year	Study quality		
		Selection	Outcome	Total (max=5)
Esposito	1984	1	1	2
Allen	1984	1	0	1
Marrie	1989	2	1	3
Fine	1990	3	1	4
Venkatesan	1990	3	1	4
Leroy	1992	1	1	2
Woodhead	1992	2	1	3
Musher	2000	2	1	3
Fernande-Sabe	2003	3	1	4
Martinez-Moragon	2004	2	1	3
Menendez	2004	2	1	3
Querol-Ribelles	2004	2	1	3
Diaz	2005	2	1	3
O'Meara	2005	2	2	4
Marrie	2005	2	1	3
Becker	2007	2	2	4
Musher	2007	3	2	5
Aliberti	2008	2	1	3
Cabre	2008	1	1	2
Ramirez	2008	2	2	4
Griffin	2013	3	2	5
Dutt	2014	3	2	5
Tang	2014	2	2	4
Bello	2015	3	1	4
Cangemi	2015	3	2	5
Chen	2015	3	2	5
Frencken	2017	2	2	4
Violi	2017	3	2	5

Cohort studies, maximum score= 7

First Author	Publication year	Study quality			
		Selection	Comparability	Outcome	Total (max=7)
Mandal	2011	3	2	2	7
Morlacchi	2011	3	2	1	6
Perry	2011	2	2	2	6
Corrales-Medina	2009	3	2	2	7
Corrales-Medina	2012	3	2	2	7
Griffin	2013	3	2	2	7
Viasus	2013	3	2	2	7

Cangemi	2014	3	2	2	7
Corrales-Medina	2014	3	2	2	7
Aliberti	2015	3	2	2	7
Shebl	2015	3	0	2	5
Violi	2015	3	1	2	6
Zhang	2016	3	2	1	6
Eurich	2017	3	2	1	6
Cilli	2018	2	2	2	6
Cangemi	2019	3	2	2	7
Pieralli	2019	3	2	2	7

Case-control studies, maximum score= 9

First Author	Publication year	Study quality			
		Selection	Comparability	Outcome	Total (max=9)
Aliberti	2016	4	1	2	7

These scores were based on three broad categories; (1) selection of the study sample, (2) comparability of the sample groups (for studies that adjust for confounders, age was *a priori* confounder) for studies investigating the risk factors for developing cardiac complications and (3) ascertainment of exposure and outcome.

4.3.3 Incidence of cardiac complications after CAP

Table 4-3 and **Fig 4-2**-**Fig 4-14** show the incidence of cardiac complications after CAP. Three studies which reported data on overall cardiac complications in-hospital were included in the meta-analysis, and the pooled proportion was 6.4% (95% CI 1.0-15.4) (**Table 4-3**, **Fig 4-2**). Two studies that were not included in the meta-analysis reported cardiac complications at different time-points; on admission: 14.7%[37], ≤7 days: 23.8%[37] and at 30 days: 8.7%.[123] Meta-analyses were conducted to summarise the incidence of individual cardiac complications after CAP; 27 studies for ACS, 25 studies for heart failure and 28 studies for arrhythmia. Across all three cardiac complications, most studies reported in-hospital incidence (**Table 4-3**). The highest pooled proportion was noted for in-hospital incidence for ACS (3.1%, 95% CI 2.2-4.0), and arrhythmia (7.9%, 95% CI 5.3-11.0), whilst for heart failure, the highest incidence was observed at 30 days (10.3%, 95%

CI 4.3-18.4). One study (n=502) was not included in the meta-analysis for incidence of arrhythmia after CAP as it reported a range of 2-4 patients developed AF in-hospital.[114]

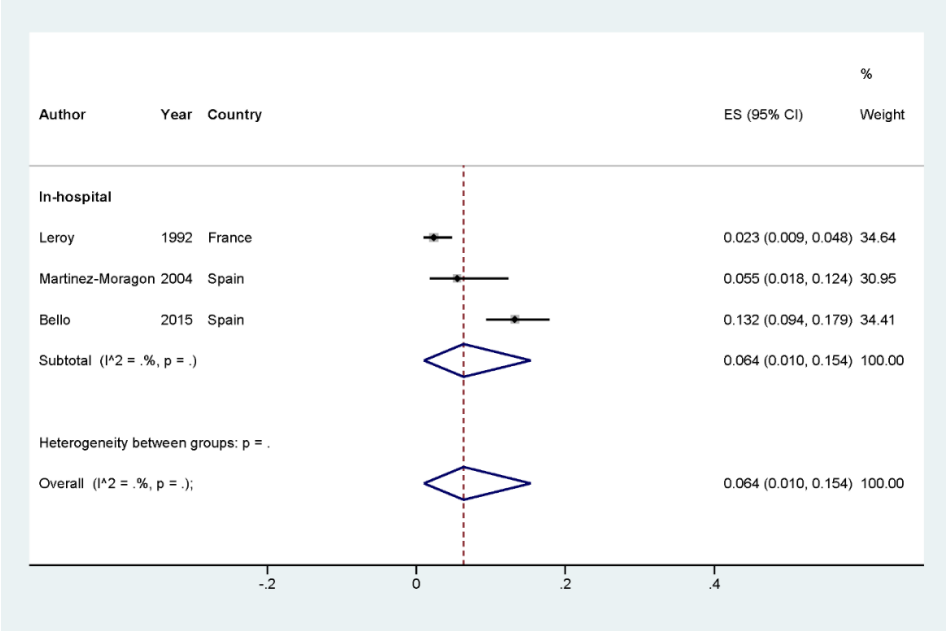
Table 4-3: Incidence of cardiac complications after CAP

Cardiac complications	Time of outcome	No of studies	Pooled proportion, % (95% CI)
Overall	In-hospital	3	6.4% (95% CI 1.0-15.4)
ACS			
	On admission	4	2.2% (95% CI 0.9-4.2)
	In-hospital	22	3.1% (95% CI 2.2-4.0)
	30 days	5	2.0% (95% CI 1.3-2.8)
	90 days	1	1.1% (95% CI 1.1-1.2)
Heart failure			
	On admission	3	3% (95% CI 1.4-5.0)
	In-hospital	19	7.7% (95% CI 4.4-11.9)
	30 days	4	10.3% (95% CI 4.3-18.4)
	90 days	2	8.6% (95% CI 8.4-8.9)
	1 year	2	3.3% (95% CI 2.8-3.7)
Arrhythmia			
	On admission	3	3.8% (95% CI 2.7-5.0)
	In-hospital	23	7.9% (95% CI 5.3-11.0)
	30 days	5	4% (95% CI 1.2-8.2)

Definition of 'overall' cardiac complications: Leroy et al[118]: 'acute coronary or ventricular insufficiency', Martinez-Moragon[122]: 'cardiac' complications and Bello et al[144]: a combination of MI, heart failure and arrhythmia. See subsequent individual forest plots.

Overall cardiac complications

Fig 4-2: Forest plot of proportions of in-hospital overall cardiac complications after community-acquired pneumonia



Definition of 'overall' cardiac complications: Leroy et al[118]: 'acute coronary or ventricular insufficiency', Martinez-Moragon[122]: 'cardiac' complications and Bello et al[144]: a combination of MI, heart failure and arrhythmia.

ACS

Fig 4-3: Forest plot of proportions of ACS on admission after community-acquired pneumonia

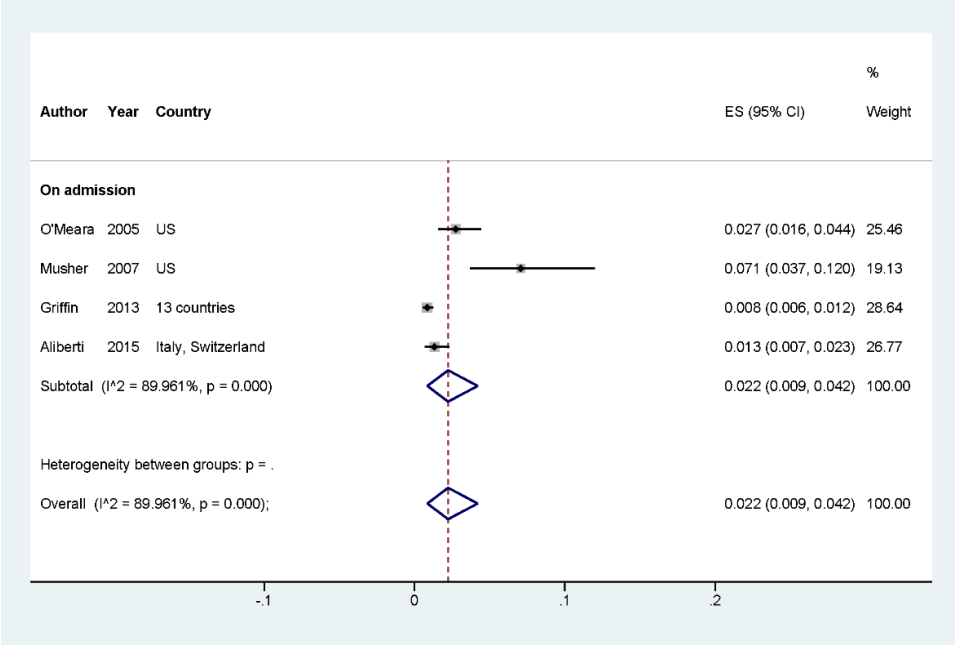


Fig 4-4: Forest plot of proportions of ACS in-hospital after community-acquired pneumonia

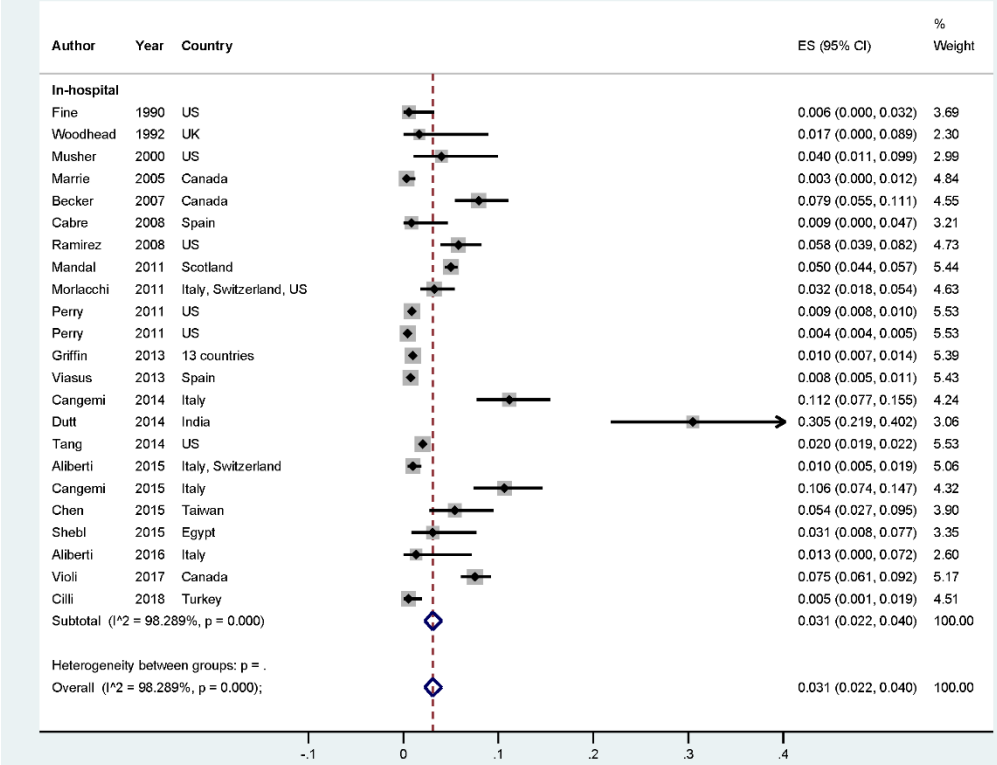


Fig 4-5: Forest plot of proportions of ACS at 30 days after community-acquired pneumonia

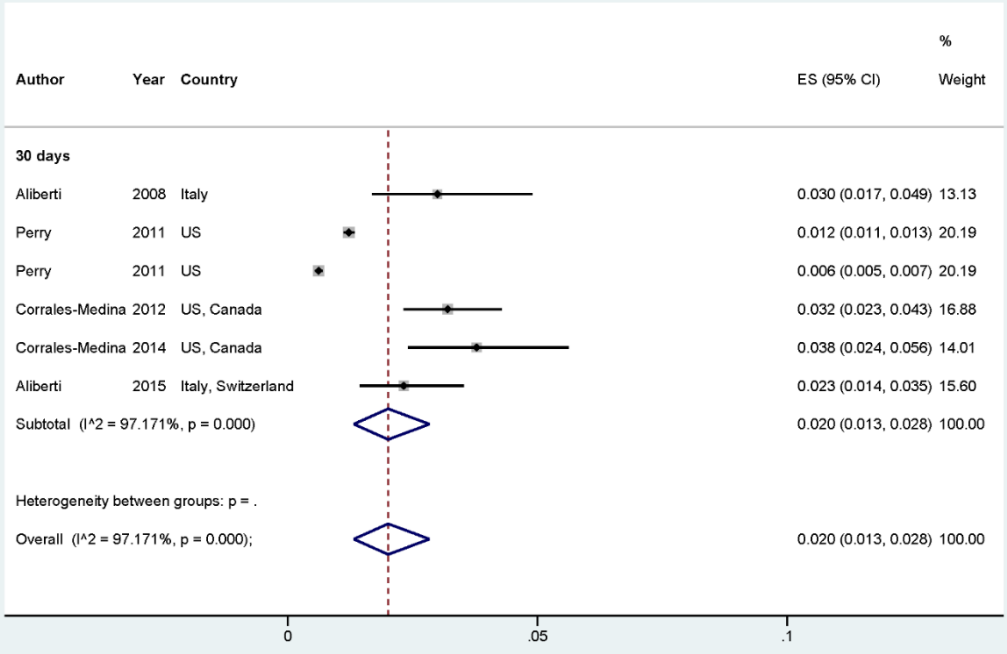
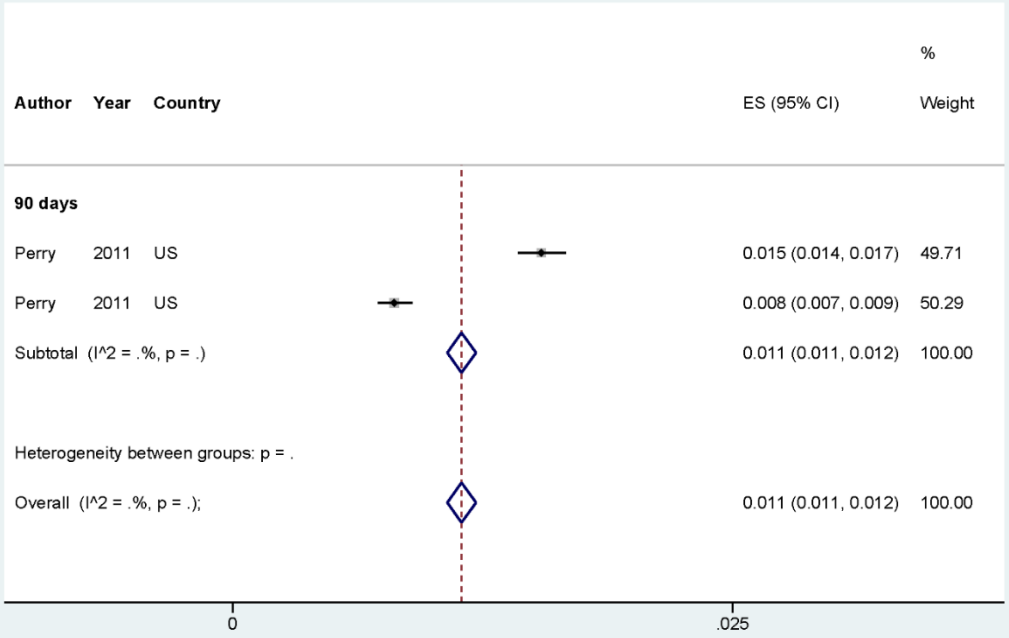


Fig 4-6: Forest plot of proportions of ACS at 90 days after community-acquired pneumonia



Heart failure

Fig 4-7: Forest plot of proportions of heart failure on admission after community-acquired pneumonia

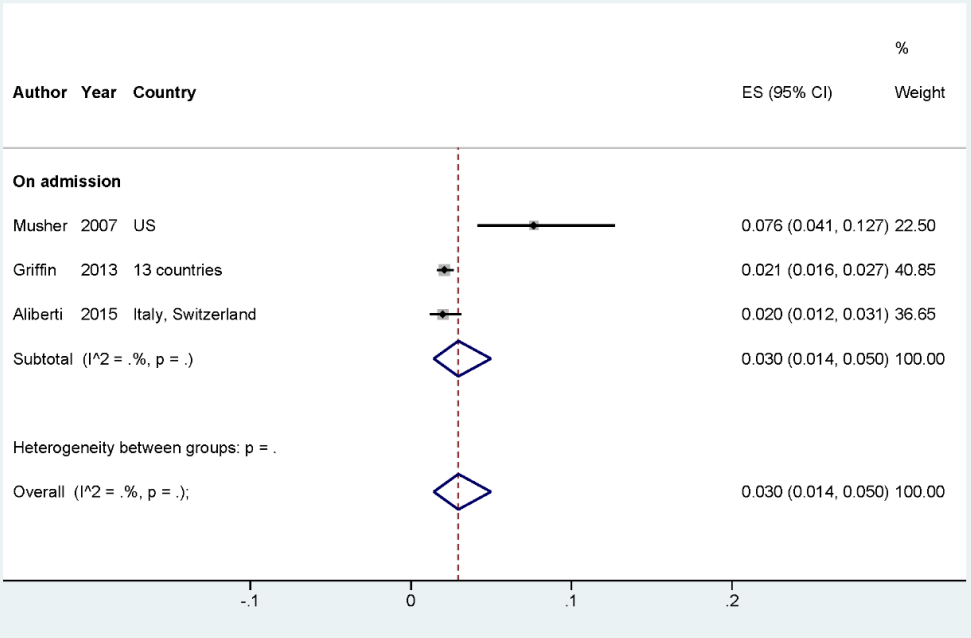


Fig 4-8: Forest plot of proportions of heart failure in-hospital after community-acquired pneumonia

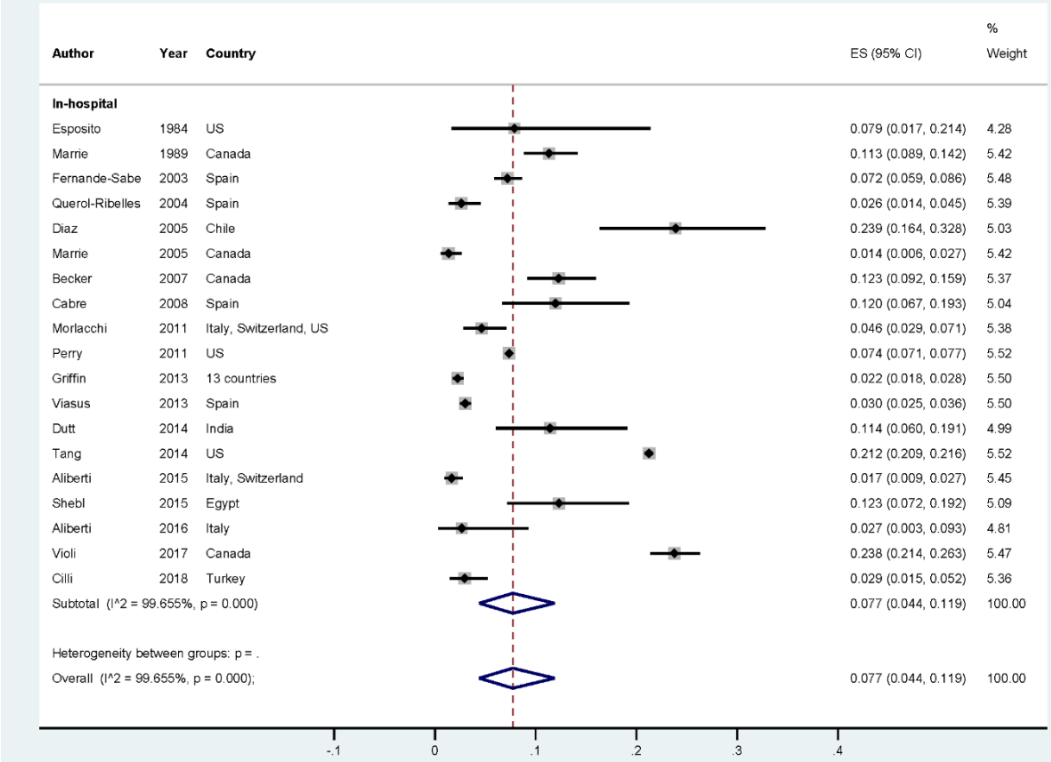


Fig 4-9: Forest plot of proportions of heart failure at 30 days after community-acquired pneumonia

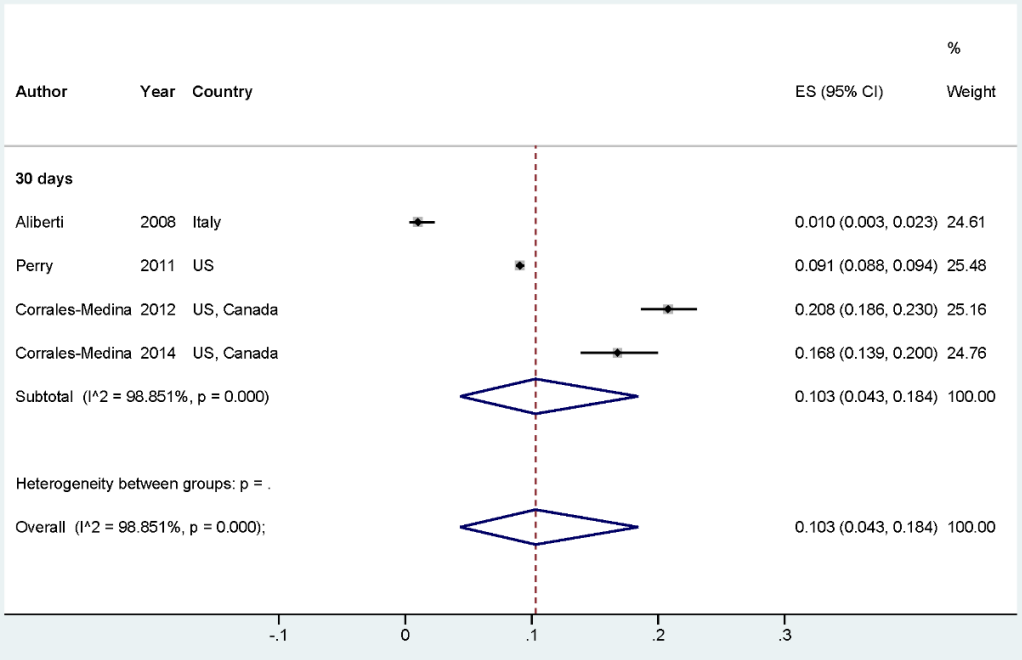


Fig 4-10: Forest plot of proportions of heart failure at 90 days after community-acquired pneumonia

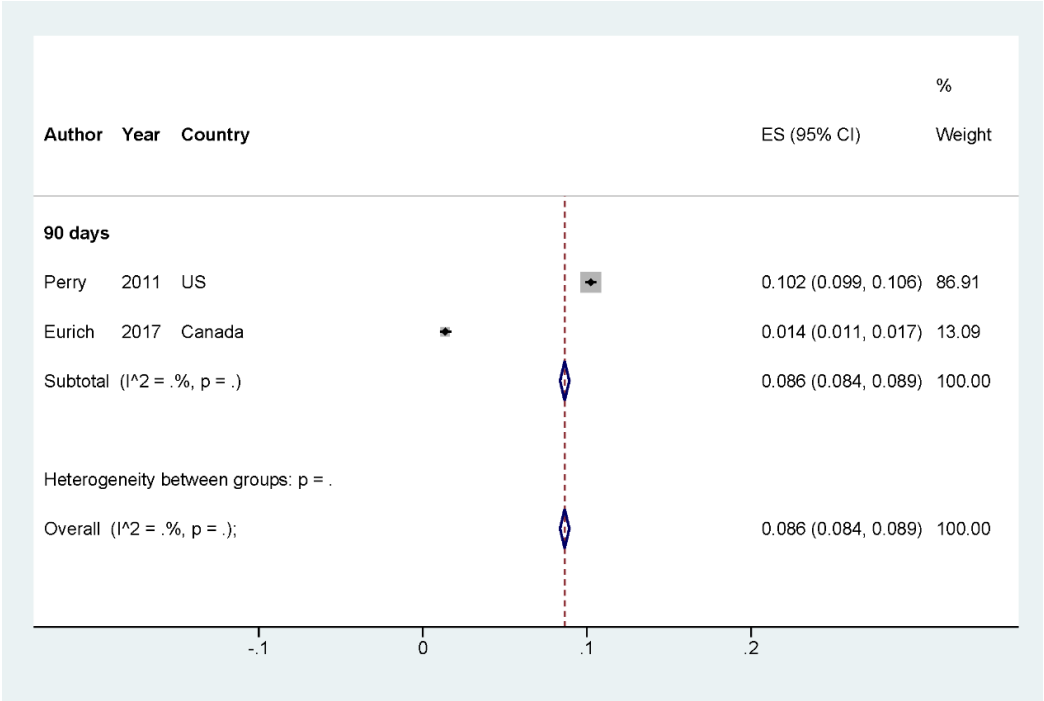


Fig 4-11: Forest plot of proportions of heart failure at 1 year after community-acquired pneumonia

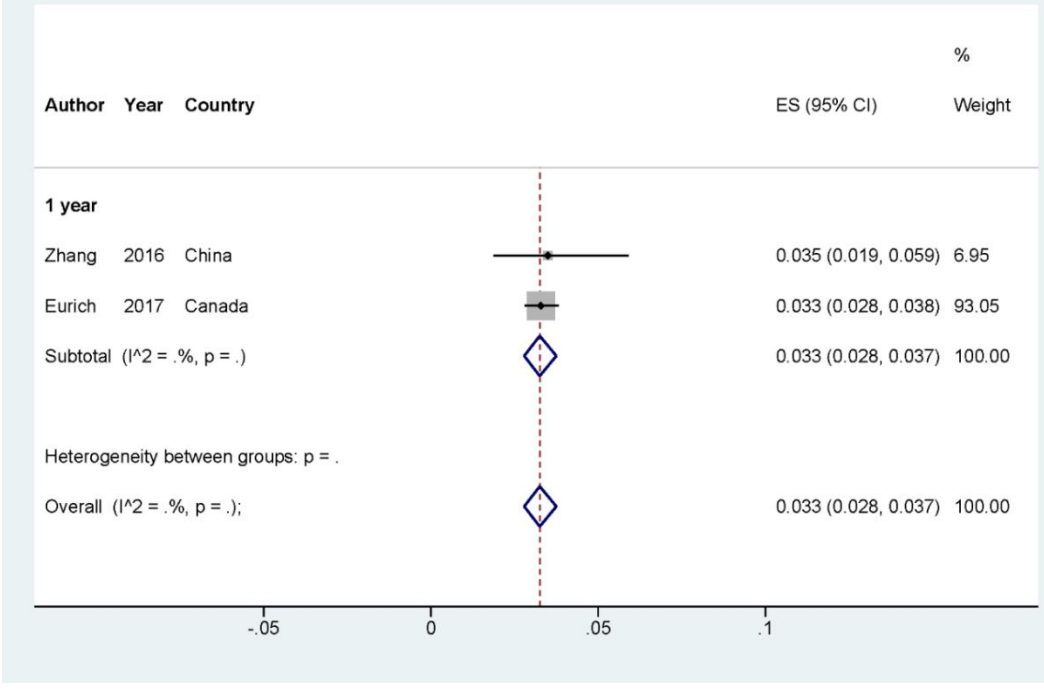


Fig 4-12: Forest plot of proportions of arrhythmia on admission after community-acquired pneumonia

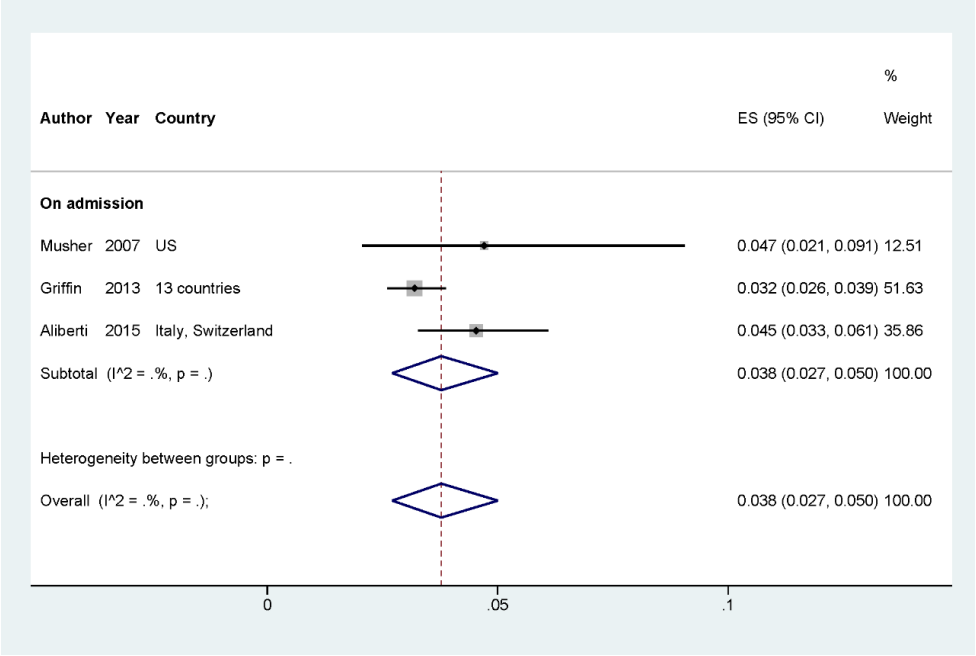


Fig 4-13: Forest plot of proportions of arrhythmia in-hospital after community-acquired pneumonia

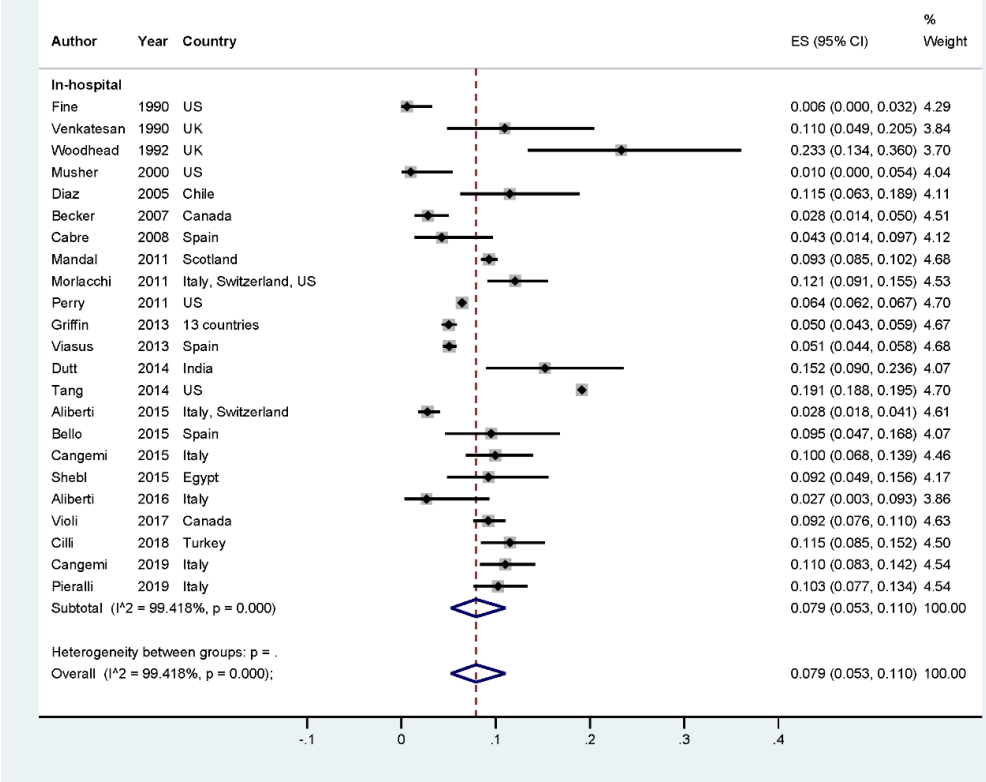
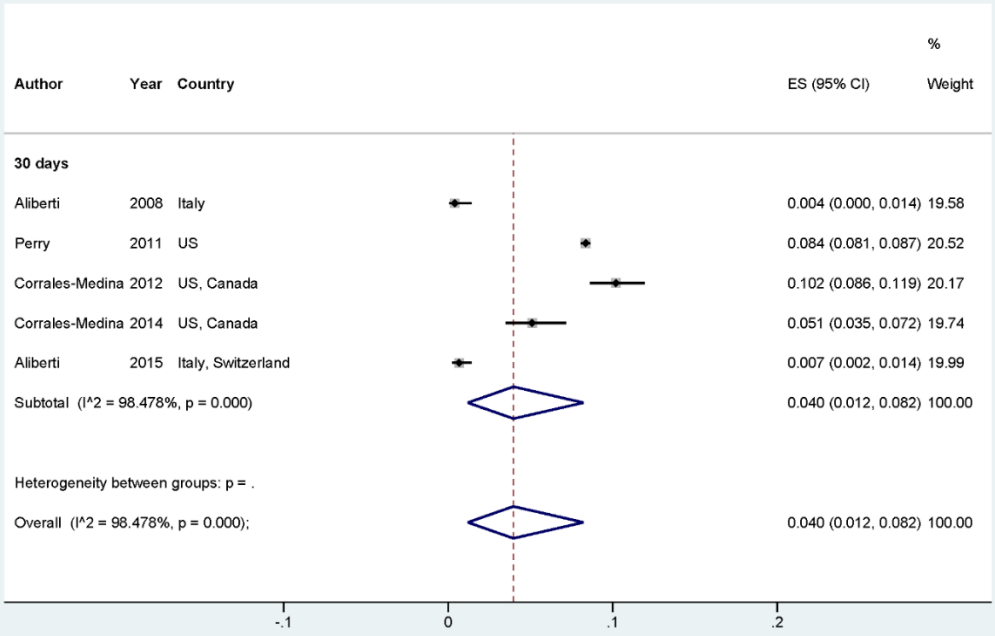


Fig 4-14: Forest plot of proportions of arrhythmia at 30 days after community-acquired pneumonia



4.3.4 Risk factors for developing cardiac complications

Thirteen studies reported risk factors of developing cardiac complications; eight studies on overall cardiac complications (**Table 4-4**), two studies on ACS, one study on heart failure and four studies on arrhythmia (**Table 4-5**). All studies reported the outcome from multivariate analysis as odds ratios with their respective confidence intervals, except for two studies; Shebl et al[147] reported univariate association and Morlacchi et al[135] reported association from multivariate analysis without the breakdown of figures. The only risk factor that could be included in the meta-analysis was age (per year increase); pooled OR 1.02, 95% CI 1.00-1.04, p=0.017, I^2=70.6%, n= 4 studies. Other than age, pre-existing cardiac disease was a commonly reported risk factor with strong association for development of cardiac complications. In addition, haemodynamic instability (tachypnoea, tachycardia and septic shock) was observed to be a strong risk factor although counterintuitively, CAP severity (measured by Pneumonia Severity Index score) was not. A number of laboratory and radiological findings were found to be associated with cardiac complications, with *K. pneumonia* and hypoalbuminaemia being the strongest predictors. Statin was associated a significantly lower risk of cardiac complications.

Table 4-4: Risk factors for developing overall cardiac complications in-hospital, at 30 days and at 1 year

Risk Factors	Author	Year	adjusted OR (95% CI)
Demographics			
Age			
per year	Corrales-Medina*	2012	1.03 (1.02-1.04)
	Griffin	2013	1.01 (1.00-1.02)
	Zhang[#]	2016	1.71 (1.07-3.84)
	Cilli	2018	1.02 (1.00-1.05)
>65	Viasus	2013	1.78 (1.28-2.47)
Gender			
Male	Griffin	2013	0.84 (0.66-1.08)
Co-morbidities			
Cardiac			
Heart failure	Corrales-Medina*	2012	4.30 (3.00-6.30)
Cardiac arrhythmia	Corrales-Medina*	2012	1.80 (1.20-2.70)
Coronary heart disease	Corrales-Medina*	2012	1.50 (1.04-2.00)
Hypertension	Corrales-Medina*	2012	1.50 (1.10-2.10)
Chronic heart disease	Viasus	2013	3.05 (2.28-4.08)
Hyperlipidaemia	Griffin	2013	2.01 (1.33-3.05)
Non-cardiac			
CKD	Viasus	2013	1.49 (0.96-2.30)
DM	Viasus	2013	1.16 (0.84-1.59)
CVD	Viasus	2013	1.04 (0.68-1.60)
Anaemia	Viasus	2013	1.22 (0.77-1.96)
History & Examination findings			
RR≥30/ min	Corrales-Medina*	2012	1.60 (1.10-2.30)
Tachycardia	Viasus	2013	1.61 (1.21-2.13)
Septic shock	Viasus	2013	1.70 (1.03-2.56)
Altered mental status	Viasus	2013	0.98 (0.67-1.41)
Pleural effusion	Corrales-Medina*	2012	1.60 (1.10-2.40)
	Cilli	2018	2.06 (0.96-4.41)
Laboratory and radiological findings			
BUN ≥30mg/dL	Corrales-Medina*	2012	1.50 (1.10-2.20)
Sodium <130 mmol/L	Corrales-Medina*	2012	1.80 (1.02-3.10)
Haematocrit <30%	Corrales-Medina*	2012	2.00 (1.30-3.20)
S. aureus	Griffin	2013	1.61 (1.02-2.86)
K. pneumoniae	Griffin	2013	2.95 (1.05-8.68)
Multilobar pneumonia	Viasus	2013	1.36 (1.03-1.81)
Hypoalbuminaemia	Viasus	2013	2.33 (1.74-3.12)
Pneumococcal pneumonia	Viasus	2013	1.39 (1.05-1.38)
sCD40L >6.0ng/ml	Cangemi	2014	1.23 (1.15-1.33)
sP-selectin >26ng/ml	Cangemi	2014	1.23 (1.14-1.33)

Serum TxB_2 >200 ng/ml	Cangemi	2014	1.08 (1.01-1.17)
Mean platelet volume	Cangemi	2014	1.03 (1.00-1.05)
pro-B-type BNP	Zhang#	2016	2.38 (1.53-6.79)
CRP	Zhang#	2016	2.43 (0.77-11.4)
ESR	Zhang#	2016	1.01 (0.69-1.31)
Cardiac troponin I	Zhang#	2016	1.83 (0.80-7.29)
Hypoalbuminaemia	Cilli	2018	2.74 (1.12-6.17)
Medications			
Statin therapy	Griffin	2013	0.52 (0.33-0.84)
Empiric macrolide therapy	Griffin	2013	0.81 (0.64-1.03)
Diuretic	Cilli	2018	2.71 (1.42-5.15)
Haloperidol	Cilli	2018	3.21 (1.64-6.30)
Vasopressor	Cilli	2018	2.71 (1.43-5.12)
Severity of CAP			
PSI score	Griffin	2013	1.02 (1.01-1.02)
	Cangemi	2014	1.00 (1.00-1.00)
	Zhang	2016	1.36 (1.02-3.21)

All studies investigated the risk factors in-hospital except Corrales-Medina* et al.[37] at 30 days and Zhang# et al.[158] at 1 year.

Letters in grey were not found to be statistically significant.

BNP: brain natriuretic peptide, CRP: C reactive protein, ESR: erythrocyte sedimentation rate, PSI: pneumonia severity index, sCD40L: soluble CD40 ligand, sP-selectin: plasma soluble P-selectin, serum TxB2: serum thromboxane B_2, DM: diabetes mellitus, CKD: chronic kidney disease, RR: respiratory rate, BUN: blood urea nitrogen,

Table 4-5: Risk factors of developing individual cardiac complications after CAP

ACS

Author	Year	Country	Time	Type of ACS	Risk factor	aOR (95% CI)	Confounders adjusted for
Mandal	2011	Scotland	In-hospital	**NSTEMI/ unstable angina**	Age≥ 65	4.73 (2.50–8.95)	Age, gender, co-morbidities, smoking history, site of care, including admission to ICU
					Previous MI	1.47 (1.01–2.17)	
				STEMI	Age≥ 65	14.0 (4.39–44.8)	
					Previous MI	1.62 (1.26–2.07)	
					COPD	2.01 (1.12–3.60)	
					Renal failure	1.90 (1.01–3.55)	
Aliberti	2015	Italy, Switzerland	In-hospital	**Acute MI**	Female	2.72 (1.02-7.25)	Age, CCF, cerebrovascular disease, acute respiratory failure on admission, nursing home residency, liver disease, CKD
					Severe sepsis on admission	4.33 (1.55-12.1)	
					Liver disease	5.82 (1.83-18.6)	

Heart failure

Author	Year	Country	Time	Risk factor	aOR (95% CI)	Confounders adjusted
Perry	2011	US	90 days	Increasing age	1.03 (1.02-1.03)	Gender, marital status, smoking, liver disease, peptic ulcer disease, unstable angina, CVD
				ICU admission	2.08 (1.85-2.34)	
				Diabetes (complicated)	1.29 (1.12-1.47)	
				Diabetes (uncomplicated)	1.36 (1.25-1.49)	
				Renal disease	1.25 (1.11-1.41)	
				Malignancy	0.78 (0.71-0.86)	
				Metastatic cancer	0.57 (0.44-0.74)	
				PVD	1.12 (1.01-1.24)	
				Hemi/ paraplegia	0.54 (0.37-0.77)	
				Rheumatoid arthritis/ collagen vascular disease	1.30 (1.06-1.60)	
				MI	1.25 (1.09-1.42)	
				Arrhythmia	1.48 (1.36-1.61)	

Arrhythmia

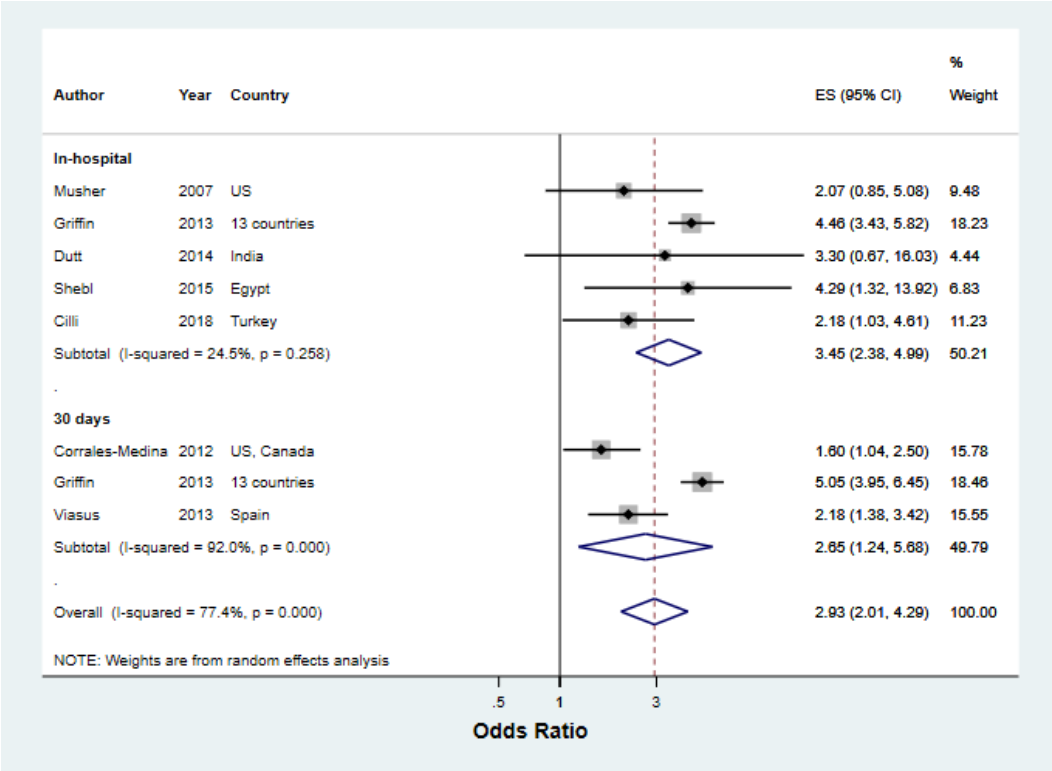
Author	Year	Country	Time	Type of arrhythmia	Risk factor	aOR (95% CI)	Confounders adjusted
Mandal	2011	Scotland	In-hospital	**AF**	Age≥ 65 Previous MI DM	5.70 (4.21–7.71) 1.37 (1.01–1.87) 1.53 (1.28–1.84)	Age, gender, co-morbidities, smoking history, site of care, including admission to ICU
Perry	2011	US	90 days	**Symptomatic bradycardia, AF, ventricular fibrillation or tachycardia, and cardiac arrest.**	Increasing age ICU admission hemi/ paraplegia Diabetes (uncomplicated) CCF	1.03 (1.02-1.03) 3.59 (3.21-4.01) 0.70 (0.57-0.85) 0.90 (0.82-0.99) 1.13 (1.03-1.24)	Gender, marital status, smoking, liver disease, peptic ulcer disease, unstable angina, CVD, PVD, renal disease, malignancy, rheumatoid arthritis/ collagen vascular diseases, MI, unstable angina
Violi	2015	Italy	In-hospital	**AF**	PSI score History of PAF Soluble Nox2 level	1.02 (1.01-1.04) 17.27(7.89-37.82) 1.04 (1.01-1.07)	High-sensitivity cardiac troponin T
Pieralli	2019	Italy	In-hospital	**AF**	CURB-65 (each point) $CHA_2DS_2VASc> 3$	1.41 (1.03-1.92) 2.30 (1.19-4.44)	Age, sex, chronic kidney disease, dementia, cancer, chronic liver disease, COPD, severity of pneumonia
Cangemi	2019	Italy	In-hospital	**AF**	Enlarged LAAi Concentric LVH Paroxysmal AF	5.41 (2.56-11.92) 2.21 (1.06-4.59) 11.69 (5.77-23.69)	Age, PSI score, hypertension, CHD, ejection fraction

PSI: pneumonia severity index, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease, AF: atrial fibrillation, PAF: paroxysmal AF, PAD: peripheral arterial disease, CKD: chronic kidney disease, RR: respiratory rate, BUN: blood urea nitrogen, BP: blood pressure, PVD: peripheral vascular disease, ICU: intensive care unit, CCF: congestive cardiac disease, LAAi: left atrial area index, LVH: left ventricular hypertrophy, MI: myocardial infarction

4.3.5 Mortality associated with cardiac complications

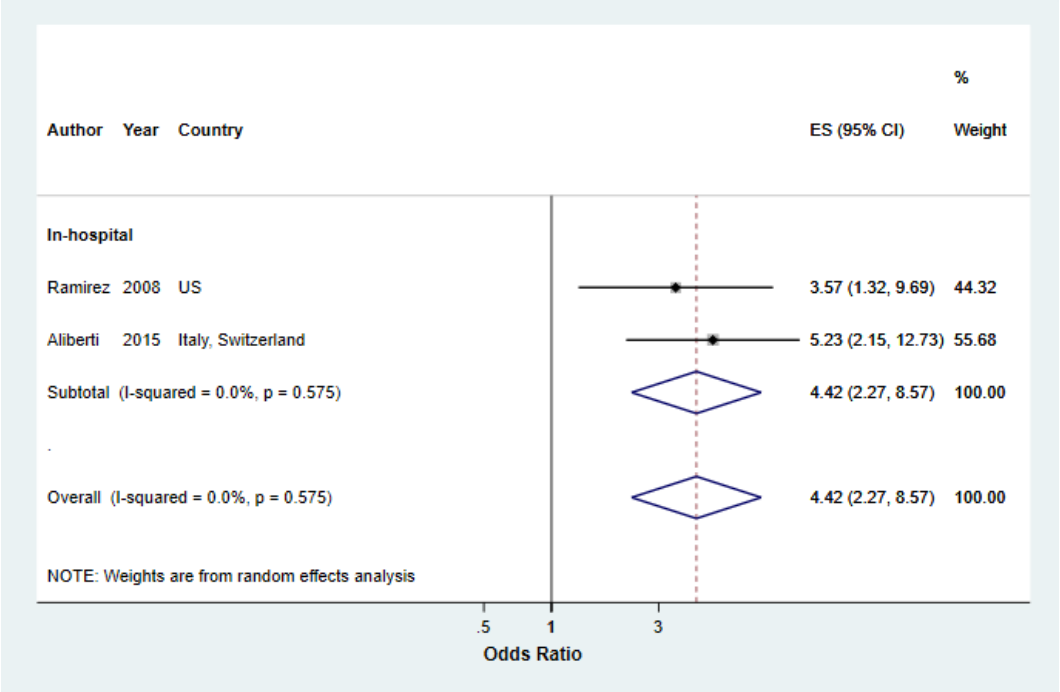
Meta-analysis of seven studies showed that patients who had cardiac complications after admission for CAP were more likely to die than those who did not (**Fig 4-15**); in-hospital: pooled OR 3.45, 95% CI 2.38-4.99, I^2=24.5%, n=5 studies and at 30 days: pooled OR 2.65, 95% CI 1.24-5.68, I^2=92%, n=3 studies). Three studies reported results from multivariate analysis[37,138,155]. One study reported adjusted hazards ratio for in-hospital cardiac complications, aHR 1.76 (95% CI 1.10-2.82, p=0.019).[145]

Fig 4-15: Forest plot of mortality associated with overall cardiac complications after CAP



Meta-analysis of two studies showed that patients who developed ACS in-hospital after admission for CAP were four times more likely to die than those who did not (pooled OR 4.42, 95% CI 2.27-8.57) (**Fig 4-16**).

Fig 4-16: Forest plot of mortality associated with ACS after CAP



Seven studies reported data on mortality associated with cardiac complications at different time points, therefore were not included in the meta-analysis (**Table 4-6**).

Table 4-6: Mortality associated with cardiac complications

Cardiac complication	Author	Year	Time of outcome	Definition	n/ N	%	aOR (95% CI)
Overall							
	Fernande-Sabe	2003	< 48 hours	Heart failure or cardiac arrhythmias	4/ 1474	0.3	-
	Zhang	2016	1 year	Cardiac	4/372	1.1	-
ACS							
	Violi	2017	In-hospital	-	7/1182	0.6	-
	Musher	2007	In-hospital	-	5/170	2.9	-
	Mandal	2011	90 days	NSTEMI/ unstable angina	-	-	1.46 (0.82-2.76)
				STEMI	-	-	1.93 (1.6-2.33)
Heart failure							
	Viasus	2013	≤ 30 days	-	-	-	3.94 (2.94-5.28)
	Musher	2007	In-hospital	-	4/170	2.4	-
	Bello	2015	30 days	-	1/265	0.4	-
			181 days- 1 year	-	2/265	0.8	-
			1- 2 years	-	3/265	1.1	-
			2- 3 years	-	2/265	0.8	-
Arrhythmia							
	Viasus	2013	≤ 30 days	-	-	-	3.36 (2.47-4.57)
	Pieralli	2019	In-hospital	-	-	-	1.79 (0.82-3.91)

4.3.6 Biomarkers

Four studies described various biomarkers as being associated with developing cardiac complications. Violi et al. found elevated serum levels of soluble Nox2, a marker of Nox2-derived oxidative stress activity, was independently associated with increased risk of developing in-hospital AF; aOR 1.04 (95% CI 1.01-1.07, p=0.01).[149] Zhang et al. found that N-Terminal pro-B-type brain natriuretic peptides (NT-pro BNP) was associated with major adverse cardiac events, which was a composite outcome of cardiac mortality, heart failure and ACS; OR 2.38 (95% CI 1.53-6.79, p=0.009).[151] Shebl et al. found three biomarkers associated with cardiac complications including procalcitonin (mean level (ng/mL) higher in those with cardiac complications than those without; 20 (SD 3.2) vs 5.2 (SD 1.3), p<0.05), NT-BNP (OR 10.47 (95% CI4.14-26.51), p<0.0001) and troponin I (OR 6.98 (95% CI 2.74-17.79), p <0.0001).[147] Cangemi et al. found platelet activation markers were associated with development of myocardial infarction (MI); plasma soluble P-selectin >26ng/ml (aOR 1.23 (95% CI 1.14-1.33), p<0.001), soluble CD40 ligand> 6ng/ml (aOR 1.23 (95% CI 1.15-1.33), p<0.001) and serum thromboxane B_2 >200 ng/ml (aOR 1.08 (95% CI 1.01-1.17), p 0.030). In addition, mean platelet volume was also found to be independently associated with MI; aOR 1.03 (95% CI 1.00-1.05), p 0.037.[139]

4.4 Discussion

4.4.1 Principal findings

To our knowledge, this is the first study to quantify the incidence of overall cardiac complications, and individual cardiac complications by time of occurrence following hospitalisation for CAP. Our study included 134,966 patients from 47 studies. The commonest incidence reported was in-hospital incidence; overall cardiac complications: 6.4%.; ACS: 3.1%, heart failure: 7.7% and arrhythmia: 7.9%. Risk factors for incident cardiac complications were explored in the past decade, and the commonly reported risk factors include older age, severity of pneumonia and pre-existing cardiac disease. Our study is the first to summarise the effect of cardiac complications after hospitalisation for CAP on mortality; patients who developed cardiac complications were approximately three times more likely to die both in-hospital (OR 3.45) and within 30 days (OR 2.65) of admission than those who did not.

4.4.2 Strengths and limitations of the study

This review comprehensively summarises the current body of knowledge regarding cardiac complications after hospitalisation for CAP and was reported in accordance with PRISMA checklist. Eligibility criteria were strictly applied to ensure identified studies only included patients with radiological confirmation of CAP. Studies with a composite outcome for cardiovascular complications were excluded, ensuring studies with only cardiac complications were included. Individual cardiac complications including ACS, new or worsening heart failure and new or worsening arrhythmia were well-defined in most studies, particularly in those conducted over the past decade. Overall, most included studies were of high quality and no language restrictions were applied.

There are a few limitations that warrant discussion. Firstly, the various was the way in which 'overall cardiac complications' was defined; studies reported it as 'cardiac' complications without a breakdown of which specific conditions were included, a combination of MI, heart failure and arrhythmia or as 'acute coronary or ventricular insufficiency'. Secondly, where available, we stratified the incidence of cardiac complications to 'on admission' and 'in-hospital' categories. It is possible that some studies may have included 'on admission' cardiac complications into the 'in-hospital' category, resulting in bias of classification. Thirdly, there was a significant heterogeneity among studies included for the meta-analyses which may be due to differences in CAP severity on admission, underlying co-morbidities, healthcare systems and other unidentified covariates. Fourthly, we included studies with patients who were hospitalised for CAP. Therefore, cardiac complications in patients with low severity CAP managed in the community were not assessed in this study.

4.4.3 Comparison with other studies

Similar to our study, Fine et al. in 1996 reported a pooled incidence rate of 8.6% (95% CI 6.4-12.3) for heart failure (n=4 studies, 232 patients) following hospitalisation for CAP, however the duration of follow-up for the occurrence of heart failure was not specified.[106] The incidence of overall cardiac complications in our study cannot be compared with previous published reviews as they included studies with cardiovascular complications. In comparison to our study, the meta-analysis by Corrales-Medina et al. reported a notably higher pooled proportion of ACS (5.3%, 95% CI 3.2-8.6) and heart failure (14.1%, 95% CI 9.3-20.6) but lower pooled proportion for arrhythmia (4.7%, 95% CI 2.4-8.9) within 30 days of admission CAP.[159] Our pooled proportion of arrhythmia is similar to that reported by Tralhao et al. (7.2%, 95% CI 5.6-9.0) but they reported higher proportions of ACS (4.5%, 95% CI 2.9-6.5) and heart failure (9.2%, 95% CI 6.7-12.2).[108]

There are two main differences between our study compared to the study by Tralhao et al.; firstly, we used the standard of two independent investigators for study selection in systematic reviews compared to a single investigator in Tralhao et al. and secondly, we stratified the meta-analyses of the incidence of cardiac complications by the time of occurrence of cardiac complications whereas Tralhao et al. did not.[160] For example, heart failure which occurred in-hospital and 90 days were combined in their analysis without making a distinction of the short- and medium/long-term risk of cardiac complications after CAP.

The differences observed between our study and the previous reviews may due to the way we stratified our study cohorts into 'on admission' and 'in-hospital' instead of combining these and change in the incidence of cardiac complications over time. The annual age- and sex-adjusted incidence rate of patients hospitalised for acute MI has remarkably reduced from 2000- 2008 by a third, partly due to improvement in the primary prevention strategies.[161] A study of 4 million patients in the UK revealed that the overall age and sex standardized incidence rate of heart failure has declined by 7% over 12 years, which would be in keeping with the decline in our pooled incidence rate.[162] However, the total number of new cases and the prevalence of heart failure has substantially increased, as a result of a rise in the aging population, better medical management of heart failure as well as other underlying co-morbidities and longer survival after heart failure diagnosis. An increasing trend of age-adjusted incidence and prevalence of atrial fibrillation was shown from the analysis of the Framingham cohort over 50 years, although this may be partly due to enhanced surveillance.[163]

In a wider context, a meta-analysis of 16 studies showed that recent influenza infection (defined as laboratory-confirmed influenza, influenza-like illness or respiratory tract

infection) was significantly more likely in AMI cases; pooled OR 2.01 (95% CI 1.47-2.76).[164] Similar to CAP, patients with influenza infection are at higher risk of cardiac complications such as new or worsening of heart failure and arrhythmia in the setting of influenza-associated myocarditis.[165]

4.4.4 Cardiac complications after CAP: mechanisms

The potential underlying mechanisms for the association of CAP and cardiac events have been extensively reviewed.[166–169] Acute coronary syndrome covers a spectrum of pathologies including unstable angina, non-ST-elevation MI (NSTEMI) and ST-elevation MI (STEMI). With regards to CAP, the two clinically relevant acute MI types are: i) Type 1 MI, which occurs secondary to plaque rupture, ulceration or fissuring resulting in thrombus formation, reducing myocardial blood flow or distal embolisation and subsequent myocardial necrosis, and ii) Type 2 MI, which is an imbalance between oxygen supply and demand caused by a condition other than coronary plaque, leading to myocardial necrosis.[170] *Streptococcus pneumonia*, the primary causative organism for CAP can drive cardiac damage via several mechanisms including causing enlargement of atherosclerotic plaques[171], directly invading the myocardium, resulting in necroptosis and apoptosis[172–174], and promoting platelet activation, resulting in procoagulant state[175]. Irrespective of the causative pathogen, CAP itself is associated with the activation of systemic coagulation, increasing the risk of thrombus formation.[176] Lung consolidation in CAP impairs gas exchange, resulting in arterial hypoxaemia, which is followed by ventilation-perfusion mismatch.[177] Upregulation of the sympathetic nervous system leads to sinus tachycardia, which increases myocardial oxygen demand (Type 2 MI) and results in a drop of coronary perfusion of the heart, precipitating the risk of ACS.[167]

Myocardial dysfunction and increased myocardial oxygen requirements also increase the cardiac workload and risk of heart failure.[178] Meta-analysis of 31 studies, mostly based on polymerase-chain reaction based diagnostic tests showed that viral infection was detected in 24.5% of patients with CAP, increasing to 44.2% in studies that obtained lower respiratory samples in >50% of the patients.[179] Viruses including influenza virus, respiratory syncytial virus and adenovirus, and to a lesser extent, bacteria such as *S. pneumoniae , H. influenzae* and *M. pneumoniae* can result in myocarditis, which could cause dilated cardiomyopathy and arrhythmia.[180]

Atrial fibrillation is the most common cardiac arrhythmia reported after CAP. Acute illness, such as CAP is a known risk factor for incident AF.[181] Pneumolysin, a pore-forming toxin produced by *S. pneumoniae* can trigger calcium overload which mediates mechanical and electrical disturbance to cardiac cells' function, resulting in arrhythmia.[182]

4.4.5 Implications for clinicians and policymakers

Mortality

In general, several studies have shown a sustained decrease in the mortality for acute MI over time due to major improvements in the delivery of care for patients with AMI, especially with more frequent use of revascularisation techniques and adjunctive evidence-based therapies.[183–188] The temporal trends in mortality after incident heart failure in the UK showed that although there was a decline in cardiovascular mortality due to considerable improvements in heart failure care, there was a significant trend of increase in non-cardiovascular deaths, particularly secondary to infections which accounted for the largest absolute increase over the 11-year period and chronic respiratory conditions.[189] Further analysis of causes of death due to infections revealed that pneumonia and influenza were important reasons which contributed to increasing

causes of death (2013 vs 2002, RR 1.59, 95% CI 1.26-1.99). In contrast, despite the continued high mortality associated with heart failure, there was no difference in mortality rate from the Framingham and Cardiovascular Health Study cohorts combined from 1990-2009 in US.[190] As for mortality in patients with incident AF between 1998-2010, a mortality reduction was seen in patients aged 55-74 (IRR 0.97, 95% CI 0.95-0.99) but no difference in those aged ≥75 years.[191]

Despite the trend of mortality reduction in some cardiac complications, our study showed that cardiac complications following CAP is associated with high risk of mortality; patients with cardiac complications were almost three times more likely to die both in-hospital and within 30 days of discharge compared to those without. In view of the associated high mortality, a high index of suspicion for cardiac complications is needed particularly in patients with suboptimal response to standard CAP treatment. These patients should be promptly investigated and managed effectively to prevent the progression of the cardiac complications.

Risk factors and biomarkers

Our study showed that the risk factors for developing cardiac complications after CAP include older age, pre-existing cardiac disease and haemodynamic instability. There is yet a validated prediction tool that clinicians can easily use to identify patients who are at high risk of developing cardiac complications when hospitalised for CAP. The role of cardiac biomarkers including troponin, BNP, procalcitonin, soluble Nox2 and platelet activation markers in predicting patients at high risk are still in its infancy.

4.4.6 Conclusion

This study substantiates that most cardiac complications occur within 30 days of hospitalisation for CAP, however only few studies evaluated the incidence of cardiac complications in the medium- (90 days) to long-term (1 year) period after CAP. The associated high mortality highlights an urgent need for tailored public health prevention approaches to improve the outcomes of patients who develop cardiac complications after CAP.

Chapter 5

Chapter 5 Matched cohort study of cardiac complications in adults hospitalised with pneumonia

5.1 Introduction

As discussed in the previous chapter, most studies from the past decade investigated the incidence of cardiac complications during hospitalisation, and only few studies investigated the incidence at 30 days and 90 days. None of these studies were from the UK.

The aims of this study were to determine the incidence of cardiac complications after hospitalisation for pneumonia at 30 days, 90 days and 1 year, and the associated risk factors, when compared to the general population in a matched cohort study in England.

5.2 Methods

5.2.1 Data sources

Hospitalisation data from Hospital Episode Statistics (HES, England), linked to the Clinical Practice Research Datalink (CPRD), a UK Government research service that provides anonymised electronic health records from general practices, and death registration data from Office for National Statistics (ONS), were used for this study.

5.2.2 Study population and follow-up

Adults aged ≥18 years with the first episode of hospitalisation for pneumonia (index date) recorded in HES between 1 July 2002 and 30 June 2017 were included. Pneumonia was defined based on J12- J18 ICD-10 codes recorded as the primary code for the first episode of hospitalisation. Patients were excluded if they a) had less than a year of time registered to the practice before admission, b) hospital-acquired pneumonia (admission for at least a day in the 10 days preceding the index admission) or c) if they had pre-

existing heart failure or arrhythmia for respective analysis. Up to 10 patients without pneumonia in CPRD were matched with each patient with pneumonia based on gender, age within a year of the index date and general practice. Controls were assigned the same index date as their matched cases. Patients for the matched cohort were eligible for inclusion if their record was labelled as acceptable by CPRD quality control.[58]

Patients were followed up from day one after the date of discharge from hospital to either the date of cardiac complications, end of data collection (30 June 2017), date of transfer out of practice, date of last data collection for the practice or date of death, whichever came first.

5.2.3 Definition of outcome

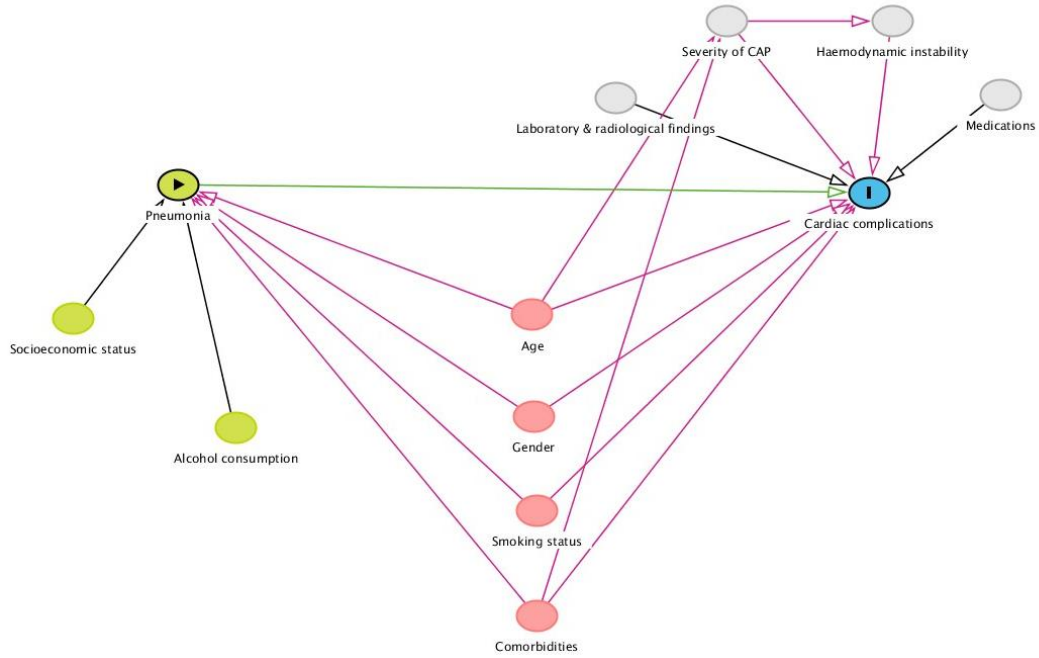
Cardiac complications were defined as i) acute coronary syndrome (ACS) including unstable angina, non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI), ii) new-onset heart failure (HF) or iii) new-onset arrhythmia using a combination of ICD-10 codes in HES and medical Read codes in CPRD (identified through medical dictionary keyword searches, previously published literature and online clinical code repositories) (Appendix 6).

5.2.4 Statistical analysis

Descriptive statistics for the patient population were calculated. Patient characteristics were stratified according to the presence or absence of cardiac complications during follow-up. 'Time to first cardiac complication' was measured at different time intervals; from the 'start date' of either day one, day 31 or day 91 after discharge from hospital to either the first hospital admission or first presentation to primary care with a cardiac complication. Incidence rates (per 1000 person-years) for each cardiac complication at

different time intervals were determined; 30 days, 31-90 days, and 91 days to 1 year. The probability of experiencing cardiac complications during follow-up was plotted using the Kaplan-Meier plot and log-rank test was used to examine any difference between the two groups of patients. Following review of published literature, directed acyclic graph (DAG) was used to identify the minimum sufficient adjustment set of confounders, which included age, gender, comorbidities (measured using Charlson Comorbidity Index), and smoking status (never smoked, ex-smokers, current smokers, unknown) (**Fig 5-1**). Multivariate competing-risks regression analysis was conducted to determine the risk of developing cardiac complications between the patients with and without pneumonia, with death as a competing event. Data management and statistical analyses were performed using StataMP/ 15.1.

Fig 5-1: Directed Acyclic Graph illustrating the association between admission for pneumonia (exposure) and developing cardiac complications (outcome).



Legend:

- exposure
- outcome
- ancestor of exposure
- ancestor of outcome
- ancestor of exposure *and* outcome
- adjusted variable
- unobserved (latent)
- other variable
- causal path
- biasing path

* Severity of pneumonia, haemodynamic instability, medications and laboratory and radiological findings were not measured in this study

5.3 Results

The overall study cohort comprised 55,808 patients with pneumonia and 438,398 age, gender and practice-matched patients without pneumonia (**Table 5-1**). The median ages of patients with and without pneumonia were 73 years (IQR 59-83) and 71 (56-80), respectively. Gender distribution was roughly equal in patient with and without pneumonia, 49.0% vs 48.6% male. Median follow-up was 1.9 years (IQR 0.5-4.3) in patients with pneumonia and 3.4 (1.6-6.3) in patients without pneumonia, with marginal difference depending on the type of cardiac complication.

Table 5-1: Characteristics of patients with and without pneumonia at 30 days, categorised by cardiac complications (ACS, heart failure and arrhythmia)

	ACS				Heart failure				Arrhythmia			
	Pneumonia n=51,855 n %		Non-pneumonia n=438,389 n %		Pneumonia n=46,911 n %		Non-pneumonia n=438,039 n %		Pneumonia n=44,849 n %		Non-pneumonia n=437,795 n %	
Age y, median (IQR)	73 (59-83)		71 (56-80)		72 (57-82)		71 (56-80)		71 (56-82)		71 (56-80)	
18-49	8099	15.6	78991	18.0	8037	17.1	78991	18.0	8041	17.9	78991	18.0
50-64	8716	16.8	83995	19.2	8388	17.9	83995	19.2	8330	18.6	83993	19.2
65-74	10332	19.9	95619	21.8	9480	20.2	95610	21.8	9196	20.5	95604	21.8
75-84	14351	27.7	119203	27.2	12396	26.4	119133	27.2	11477	25.6	119074	27.2
≥85	10357	20.0	60581	13.8	8610	18.4	60310	13.8	7805	17.4	60133	13.7
Gender												
Male	25424	49.0	213008	48.6	22840	48.7	212813	48.6	21788	48.6	212683	48.6
Female	26431	51.0	225381	51.4	24071	51.3	225226	51.4	23061	51.4	225112	51.4
Smoking status												
Never	11459	22.1	137513	31.4	10446	22.3	137400	31.4	9942	22.2	137454	31.4
Ex	8059	15.5	66784	15.2	7050	15.0	66670	15.2	6589	14.7	66731	15.2
Current	31047	59.9	211348	48.2	28212	60.1	211253	48.2	27126	60.5	211314	48.2
Unknown	1290	2.5	22744	5.2	1203	2.6	22716	5.2	1192	2.7	22742	5.2
Charlson Comorbidity Index												
0	13110	25.3	221822	50.6	13110	27.9	221764	50.6	12477	27.8	221713	50.6
1	11547	22.3	82972	18.9	11142	23.8	82912	18.9	10402	23.2	82864	18.9
2	9062	17.5	60135	13.7	8239	17.6	60056	13.7	7704	17.2	60009	13.7
3	6974	13.4	35659	8.1	6064	12.9	35596	8.1	5719	12.8	35555	8.1
4	4519	8.7	18287	4.2	3595	7.7	18249	4.2	3553	7.9	18225	4.2
≥5	6643	12.8	19514	4.5	4761	10.1	19462	4.4	4994	11.1	19429	4.4

The most common cardiac complication after hospitalisation for pneumonia was new-onset heart failure, followed by new-onset arrhythmia and ACS. The proportion of cardiac complications is listed in **Table 5-2**.

Table 5-2: The proportion of ACS, heart failure and arrhythmia after hospitalisation for pneumonia.

Cardiac disease	n (%)			Cumulative Total
	30 days	31-90 days	91-365 days	
ACS	282 (0.5)	196 (0.4)	534 (1.0)	1012 (1.8)
Heart failure	703 (1.3)	553 (1.0)	949 (1.7)	2205 (3.9)
Arrhythmia	693 (1.2)	353 (0.6)	651 (1.2)	1697 (3.0)

The incidence rates of all cardiac complications were the highest within 30 days of discharge following hospitalisation for pneumonia, after which the rate declined (**Table 5-3**).

Table 5-3: Incidence rates (per 1000 person-years) of ACS, HF and arrhythmia after hospitalisation for pneumonia.

Cardiac disease	Incidence rate (/1,000 person-years) (95 % CI)		
	30 days	31-90 days	91-365 days
ACS	64.3 (57.2-72.3)	23.2 (20.1-26.6)	15.9 (14.6-17.3)
Heart failure	161.0 (149.6-173.4)	65.8 (60.5-71.5)	28.6 (26.9-30.5)
Arrhythmia	158.9 (147.5-171.2)	42.0 (37.9-46.7)	19.6 (18.2-21.2)

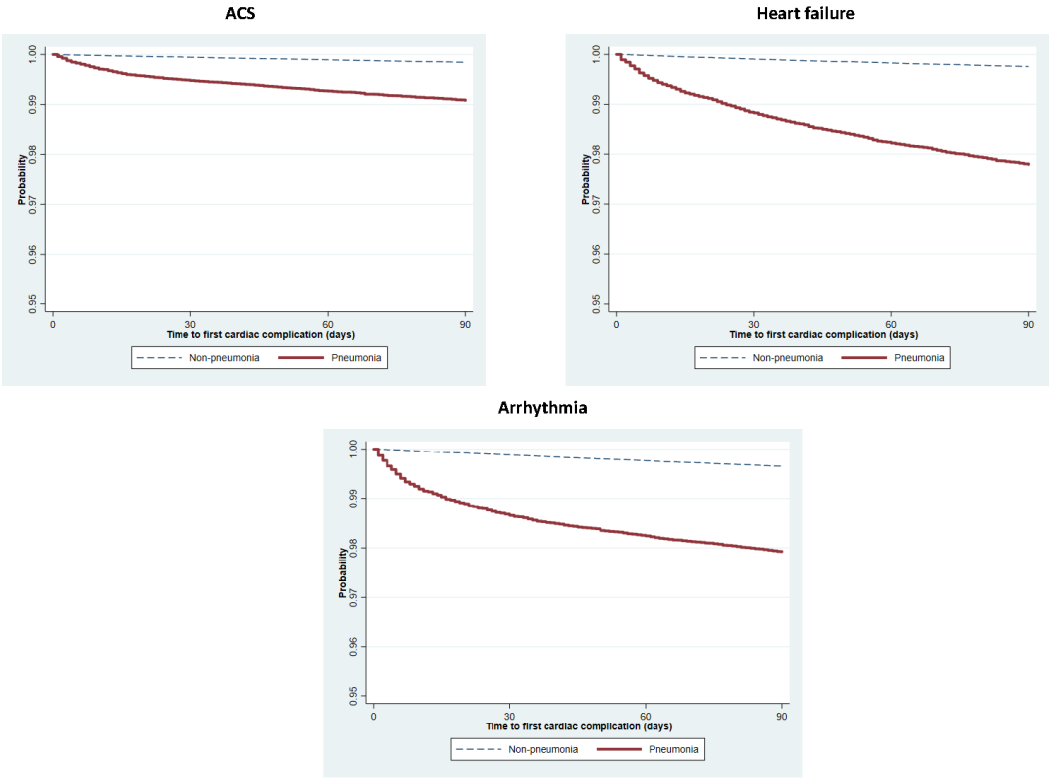
In addition to pneumonia, these cardiac complications may contribute to the number of years life lost to disease and the number of years lived with disability as a result of the disease. The absolute increase in events (per 10,000 patient) was observed to be greater in the short-term compared to long-term; 257 events between 1-30 days vs 266 events between 91 days- 1 year (**Table 5-4**).

Table 5-4: Absolute increase in events (per 10,000 patients) in patients with pneumonia compared to those without pneumonia in the short and long-term.

	1-30 days	91 days-1 year
ACS	42	67
Arrhythmia	115	60
Heart failure	100	139
Total	257	266

In view of the declining trend observed with time, the subsequent results focus on cardiac complications that occur at 30 days and 90 days. The time to first recorded cardiac complication was significantly different between the patients with and without pneumonia (log-rank test: $p < 0.0001$) (**Fig 5-2**).

Fig 5-2: Kaplan-Meier plots of time to first cardiac complication in patients with and without pneumonia.



Incidence rates by year of admission for pneumonia showed an overall decreasing trend for ACS, whilst an increasing trend for arrhythmia from 2002-2017 (**Fig 5-3**). For heart failure, there was a significant decrease in incidence rate from 2002-2006, after which there was an increasing trend until 2016/17.

Fig 5-3: Incidence rate for all cardiac complications by year of admission for pneumonia.

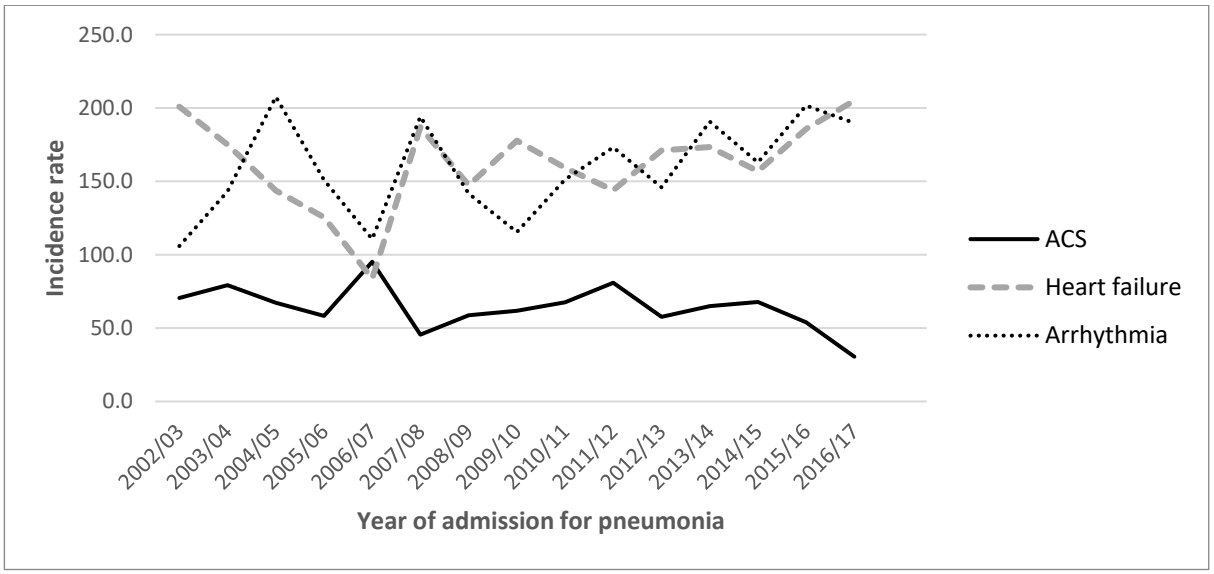


Table 5-7- **Table 5-7** show that patients with pneumonia were significantly at higher risk of developing cardiac complications than those without, with greater risk observed within 30 days compared to 90 days. Age was a strong independent risk factor for developing any cardiac complications. Higher Charlson Comorbidity Index score was also identified as an independent risk factor across all cardiac complications.

At 30 days, patients with pneumonia were almost six times more likely to develop ACS compared to those without pneumonia; sHR 5.82 (95% CI 4.75-7.14) (**Table 5-5**). The risk lowered by more than 50% at 90 days. Males were more likely to develop ACS at 90 days, not 30 days. Current smoking was an independent risk factor for developing ACS.

Table 5-5: Competing-risks regression for the risk of developing ACS in patients with and without pneumonia, and the factors associated with the risk of developing ACS.

	ACS											
	30 days						90 days					
	Crude sHR (95% CI)		p value	Adjusted sHR (95% CI)		p value	Crude sHR (95% CI)		p value	Adjusted sHR (95% CI)		p value
Non-pneumonia				1.00	(Reference)					1.00	(Reference)	
Pneumonia				5.82	(4.75-7.14)	<0.001				2.45	(2.00-2.98)	<0.001
Age												
18-49	1.00			1.00			1.00			1.00		
50-64	8.61	(3.42-21.66)	<0.001	7.04	(2.79-17.77)	<0.001	7.19	(3.44-15.02)	<0.001	5.59	(2.66-11.73)	<0.001
65-74	13.09	(5.30-32.28)	<0.001	8.94	(3.57-22.36)	<0.001	12.89	(6.31-26.34)	<0.001	7.97	(3.86-16.47)	<0.001
75-84	21.54	(8.86-52.37)	<0.001	13.39	(5.39-33.27)	<0.001	14.99	(7.38-30.42)	<0.001	8.30	(4.02-17.17)	<0.001
≥85	25.20	(10.31-61.57)	<0.001	16.35	(6.54-40.90)	<0.001	23.13	(11.36-47.11)	<0.001	13.92	(6.66-29.12)	<0.001
Gender												
Male	1.00						1.00					
Female	0.87	(0.72-1.06)	0.162	0.86	(0.70-1.04)	0.119	0.60	(0.50-0.71)	<0.001	0.57	(0.48-0.68)	<0.001
Smoking status												
Never	1.00						1.00					
Ex	1.57	(1.15-2.14)	0.004	1.16	(0.84-1.59)	0.366	1.73	(1.33-2.26)	<0.001	1.16	(0.88-1.51)	0.292
Current	1.54	(1.20-1.97)	0.001	1.42	(1.10-1.82)	0.006	1.50	(1.21-1.86)	<0.001	1.28	(1.03-1.59)	0.028
Unknown	0.65	(0.31-1.34)	0.242	0.91	(0.44-1.91)	0.81	0.50	(0.26-0.99)	0.047	0.72	(0.37-1.44)	0.357
Charlson Comorbidity Index												

0	1.00						1.00					
1	1.83	(1.31-2.57)	<0.001	1.37	(0.96-1.94)	0.079	2.57	(1.94-3.42)	<0.001	1.98	(1.48-2.65)	<0.001
2	3.21	(2.35-4.39)	<0.001	1.97	(1.41-2.76)	<0.001	4.12	(3.14-5.42)	<0.001	2.64	(1.97-3.53)	<0.001
3	2.93	(2.05-4.19)	<0.001	1.66	(1.14-2.42)	0.009	4.41	(3.25-5.97)	<0.001	2.62	(1.89-3.63)	<0.001
4	5.59	(3.94-7.93)	<0.001	2.98	(2.05-4.35)	<0.001	5.31	(3.78-7.46)	<0.001	2.96	(2.06-4.25)	<0.001
≥5	6.21	(4.48-8.63)	<0.001	3.26	(2.27-4.67)	<0.001	7.57	(5.60-10.23)	<0.001	4.11	(2.94-5.74)	<0.001

Patients with pneumonia were approximately nine times more likely to develop heart failure at 30 days compared to those without pneumonia; sHR 8.78 (95% CI 7.55-10.22) (**Table 5-6**). Similar to ACS, the risk significantly lowered at 90 days but by just under 50%. Unlike ACS, males were more likely to develop heart failure at both 30 days and 90 days. Current smoking was not an independent risk factor for heart failure.

Table 5-6: Competing-risks regression for the risk of developing heart failure in patients with and without pneumonia, and the factors associated with the risk of developing heart failure.

	Heart failure											
	30 days						90 days					
	Crude sHR (95% CI)		p value	Adjusted sHR (95% CI)		p value	Crude sHR (95% CI)		p value	Adjusted sHR (95% CI)		p value
Non-pneumonia				1.00	(Reference)					1.00	(Reference)	
Pneumonia				8.78	(7.55-10.22)	<0.001				4.85	(4.20-5.60)	<0.001
Age												
18-49	1.00			1.00			1.00			1.00		
50-64	5.51	(2.82-10.78)	<0.001	4.43	(2.25-8.69)	<0.001	2.55	(1.41-4.61)	0.002	1.96	(1.08-3.56)	0.027
65-74	12.93	(6.82-24.51)	<0.001	8.50	(4.43-16.28)	<0.001	7.09	(4.15-12.11)	<0.001	4.26	(2.46-7.36)	<0.001
75-84	20.91	(11.14-39.24)	<0.001	12.36	(6.48-23.57)	<0.001	17.71	(10.58-29.65)	<0.001	9.20	(5.39-15.73)	<0.001
≥85	29.03	(15.42-54.65)	<0.001	17.63	(9.22-33.70)	<0.001	25.58	(15.22-42.97)	<0.001	13.50	(7.85-23.20)	<0.001
Gender												
Male	1.00						1.00					
Female	0.86	(0.75-0.99)	0.039	0.80	(0.70-0.92)	0.002	0.87	(0.76-0.99)	0.041	0.79	(0.69-0.90)	0.001
Smoking status												
Never	1.00						1.00					
Ex	1.45	(1.17-1.80)	0.001	1.02	(0.82-1.27)	0.878	1.63	(1.33-1.99)	<0.001	1.10	(0.90-1.35)	0.354
Current	1.19	(1.00-1.42)	0.046	1.09	(0.92-1.31)	0.317	1.22	(1.04-1.44)	0.018	1.13	(0.95-1.34)	0.158
Unknown	0.77	(0.48-1.22)	0.265	1.17	(0.73-1.87)	0.514	0.45	(0.26-0.77)	0.004	0.72	(0.42-1.25)	0.242
Charlson Comorbidity Index												
0	1.00						1.00					

1	2.97	(2.31-3.81)	<0.001	2.22	(1.71-2.88)	<0.001	3.37	(2.63-4.32)	<0.001	2.38	(1.84-3.07)	<0.001
2	3.79	(2.94-4.88)	<0.001	2.26	(1.73-2.95)	<0.001	4.74	(3.70-6.07)	<0.001	2.57	(1.98-3.34)	<0.001
3	5.04	(3.86-6.57)	<0.001	2.77	(2.09-3.68)	<0.001	7.13	(5.55-9.17)	<0.001	3.48	(2.66-4.56)	<0.001
4	5.82	(4.33-7.81)	<0.001	3.01	(2.20-4.12)	<0.001	9.15	(6.96-12.02)	<0.001	4.10	(3.05-5.50)	<0.001
≥5	8.82	(6.77-11.51)	<0.001	4.57	(3.43-6.07)	<0.001	11.79	(9.13-15.21)	<0.001	5.22	(3.96-6.88)	<0.001

Compared to all cardiac complications, the highest risk was for developing arrhythmia at 30 days; sHR 9.68, 95% CI 8.49-11.04 (**Table 5-7**). The risk at 90 days was a quarter of that observed at 30 days. Similar to ACS, males were more likely to develop arrhythmia at 90 days, not 30 days. Current smoking was not an independent risk factor for arrhythmia, similar to heart failure.

Table 5-7: Competing-risks regression for the risk of developing arrhythmia in patients with and without pneumonia, and the factors associated with the risk of developing arrhythmia.

	Arrythmia											
	30 days						90 days					
	Crude sHR (95% CI)		p value	Adjusted sHR (95% CI)		p value	Crude sHR (95% CI)		p value	Adjusted sHR (95% CI)		p value
Non-pneumonia				1.00	(Reference)					1.00	(Reference)	
Pneumonia				9.68	(8.49-11.04)	<0.001				2.62	(2.27-3.02)	<0.001
Age												
18-49	1.00			1.00			1.00			1.00		
50-64	5.66	(3.28-9.78)	<0.001	5.26	(3.04-9.11)	<0.001	11.01	(5.08-23.82)	<0.001	9.78	(4.51-21.19)	<0.001
65-74	12.85	(7.62-21.67)	<0.001	11.42	(6.74-19.35)	<0.001	26.88	(12.67-57.03)	<0.001	21.67	(10.18-46.15)	<0.001
75-84	19.51	(11.66-32.65)	<0.001	17.21	(10.21-29.03)	<0.001	53.00	(25.15-111.68)	<0.001	41.03	(19.34-87.06)	<0.001
≥85	21.79	(12.96-36.64)	<0.001	19.71	(11.62-33.40)	<0.001	65.36	(30.92-138.13)	<0.001	53.03	(24.90-112.93)	<0.001
Gender												
Male	1.00						1.00					
Female	1.02	(0.91-1.16)	0.701	0.94	(0.83-1.06)	0.297	0.86	(0.77-0.97)	0.01	0.77	(0.69-0.86)	<0.001
Smoking status												
Never	1.00						1.00					
Ex	1.28	(1.06-1.54)	0.011	1.01	(0.83-1.22)	0.921	1.60	(1.36-1.88)	<0.001	1.17	(0.99-1.38)	0.066
Current	1.05	(0.91-1.22)	0.521	1.09	(0.93-1.27)	0.275	1.10	(0.96-1.27)	0.156	1.10	(0.96-1.27)	0.168
Unknown	0.52	(0.33-0.82)	0.005	0.64	(0.40-1.01)	0.053	0.32	(0.19-0.52)	<0.001	0.40	(0.24-0.67)	<0.001
Charlson Comorbidity Index												
0	1.00						1.00					

1	1.84	(1.53-2.21)	<0.001	1.32	(1.09-1.59)	0.004	1.88	(1.58-2.24)	<0.001	1.28	(1.07-1.53)	0.006
2	2.50	(2.08-3.01)	<0.001	1.42	(1.17-1.72)	<0.001	2.93	(2.48-3.47)	<0.001	1.51	(1.27-1.80)	<0.001
3	2.16	(1.73-2.69)	<0.001	1.12	(0.89-1.41)	0.326	3.32	(2.76-4.01)	<0.001	1.55	(1.27-1.89)	<0.001
4	3.24	(2.57-4.09)	<0.001	1.59	(1.24-2.02)	<0.001	3.68	(2.95-4.59)	<0.001	1.58	(1.25-1.99)	<0.001
≥5	2.08	(1.62-2.67)	<0.001	1.02	(0.78-1.32)	0.887	3.41	(2.74-4.25)	<0.001	1.44	(1.15-1.82)	0.002

5.4 Discussion

5.4.1 Principal findings

This is the first study in the UK to investigate the incidence of, and risk factors for developing cardiac complications after hospitalisation for pneumonia. The most common cardiac complication was new-onset heart failure, followed by new-onset arrhythmia and ACS. The incidence rates of all cardiac complications were the highest within 30 days of discharge. Compared to age, gender and practice-matched patients without pneumonia, those with pneumonia were significantly at higher risk of developing all cardiac complications, with the highest risk observed for developing arrhythmia at 30 days after discharge. The independent risk factors for developing cardiac complications include increasing age and higher Charlson Comorbidity Index score.

5.4.2 Strengths and limitations of the study

A key strength of this study is the large sample size of over 55,000 patients, that is representative of the English population with long-term follow-up. The usage of two large validated medical record databases, HES-CPRD linkages enabled patients with cardiac complications who presented to both primary and secondary care to be accurately identified and captured in this study. In addition, compared to previous studies which present simple proportions, we have presented the incidence rates of cardiac complications which take into account the patients who 'dropped-out' of the study, therefore reflecting a more accurate occurrence of the cardiac complications during follow-up.

However, there are a few limitations that warrant discussion. Firstly, HES data are from England, therefore, the results from this study may not be generalisable to the rest of the

UK. Secondly, although considerable efforts were taken to ensure data quality, we cannot fully exclude the possibility of information bias from miscategorisation of the study exposure (pneumonia), confounders (particularly smoking status) and outcomes (ACS, heart failure and arrhythmia) in the HES-CPRD dataset. Of those who had ICD-10 code of pneumonia within HES, a third of cases did not have evidence of pneumonia on the chest radiograph (CXR).[30] Equally, CXR was found to have been classified as 'normal' when chest CT has shown parenchymal infiltrates confirming pneumonia in a third of suspected CAP cases.[192] This suggests that it is possible for a proportion of cases thought to have been miscoded as pneumonia due to normal CXR were not miscoded. As for the diagnosis of cardiac complications in HES-CPRD, high validity was found in both datasets.[62,193,194]

5.4.3 Comparison with other studies

The proportions of cardiac complications reported in this study were significantly lower compared to previous published studies. In the previous chapter, the 30-day incidence for ACS, heart failure and arrhythmia were 2.0% (95% CI 1.3-2.8, n=5 studies), 10.3% (95% CI 4.3-18.4, n= studies) and 4% (95% CI 1.2-8.2, n=5 studies) respectively.[195] A possible explanation for the difference seen may be due to marked differences in study methodology (administrative data vs predominantly clinical data) and healthcare systems (studies included in the meta-analysis were from country with non-universal insurance system: US, country with universal private health insurance system: Switzerland, and countries with universal government-funded health system similar to the UK: Canada and Italy). The latter may impact access to, and utilisation of healthcare services, thus impacting the detection and recording of cardiac complications. This emphasizes the importance of country-specific data. In the same meta-analysis, the 90-day incidence for ACS and heart failure were high; 1.1% (95% CI 1.1-1.2, n=1 study) and 8.6% (95% CI 8.4-

8.9; n=2 studies) respectively. It is noteworthy that the 90-day incidence was measured from date of discharge as opposed to 31-90 days as in this study. In addition, these studies used older data (up to 2002 with a maximum study period of six years), compared to this study which had latest data up to 2017 with over twice the study period. Over the 15-year study period, there has been considerable improvement in primary prevention strategies resulting in lower incidence of ACS observed, similar to that found by Reynolds et al.[161] However enhanced surveillance and better management of cardiac disease as well as underlying comorbidities in the aging population may have led to a higher incidence of heart failure and arrhythmia, in keeping with previous published literature.[162,163]

The strongest risk factor for developing cardiac complications was age. This is in keeping with four prior studies of patients with pneumonia, irrespective of follow-up duration.[136,138,151,155] In contrast to Griffin et al. who found that males were not associated with the risk of developing cardiac complications during hospitalisation, we found males had a higher risk, particularly at 90 days.[137] Other independent risk factors include current smoking (for ACS) and higher Charlson Comorbidity Index score which have not been previously investigated. Previous studies have shown underlying cardiac comorbidities such as heart failure, arrhythmia, coronary heart disease, hypertension, chronic heart disease and hyperlipidaemia were associated with an increased risk whilst non-cardiac comorbidities such as diabetes, chronic kidney disease, anaemia and cerebrovascular disease were not associated with the development of cardiac complications.[136–138]

In the content of current COVID-19 pandemic, it is noteworthy that studies have reported similar cardiac complications of ACS, heart failure and arrhythmia.[196] Possible

mechanisms include direct cardiotoxicity, ACS secondary to plaque rupture or thrombosis (Type I MI) or supply-demand mismatch (Type II MI), myocardial injury due to disseminated intravascular complications and non-ischaemic myocardial injury (myocarditis, stress-induced cardiomyopathy, or cytokine release syndrome).[197] Acute myocardial injury, defined by elevated serum levels of troponin T (>99th percentile upper reference limit) carries poorer prognosis with greater complications (acute respiratory distress syndrome, acute kidney injury, electrolyte disturbance and coagulation disorders) and higher mortality.[198,199]

5.4.4 Implications for clinicians and policymakers

Most cardiac complications occur within 30 days of hospitalisation for CAP, with declining rate at 90 days and subsequently a year after CAP. Concerted efforts should be taken to identify patients at risk of developing cardiac complications, especially within 30 days of discharge as prevention is the key to reducing the associated burden to patients. Further research is warranted to develop and evaluate a risk prediction tool to provide individualized risk assessment which could identify those at higher risk of developing cardiac complications. Evidence- based risk stratification policy could be used to implement strategies, including provision of pneumococcal and influenza vaccination to prevent the occurrence of pneumonia and reduce the risk of cardiac complications, particularly in the aging population with multiple comorbidities.[200–204] The role of potential adjunctive therapies such as statins, antiplatelet drugs and angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), in order to prevent the occurrence of cardiac complications is yet to be established.[166]

An important and modifiable risk factor for ACS in patients hospitalised with pneumonia is current smoking. Tobacco smoking is associated with an increased risk of developing

cardiovascular disease as well as pneumonia, with a well-described dose-dependent association.[205,206] Current tobacco smoking status at index hospitalisation for pneumonia has also been shown to be independently associated with a higher risk of recurrent pneumonia.[207] This highlights the importance of implementing effective smoking cessation interventions as a key component of pneumonia management, in accordance with the NHS Long Term Plan.[93] Patients should be referred to a Stop Smoking Service during hospitalisation for pneumonia and receive subsequent continuous support upon discharge.

5.5 Conclusion

This study corroborates that most cardiac complications occur within 30 days of hospitalisation for CAP, and further demonstrates that the rates decline at 90 days and subsequently a year after CAP. The focus should be on identifying patients at risk, particularly early after hospitalisation for CAP and targeting strategies to prevent cardiac complications, alongside addressing modifiable risk factor of tobacco smoking.

Chapter 6

Chapter 6 Effect of tobacco smoking on the risk of developing community acquired pneumonia: A systematic review and meta-analysis

6.1 Introduction

Tobacco smoking is a major cause of morbidity and mortality in high income countries and is an important risk factor for CAP.[208] Tobacco smoking impairs mucociliary clearance by causing an increase in mucous production and number of abnormal cilia alongside reduction of ciliary beat frequency.[209] Piatti *et al.* found that tobacco smoking modifies buccal epithelial surfaces which causes increased pneumococcal adherence compared to never smokers.[210] Greater bacterial adherence may lead to greater oropharyngeal colonisation and hence a greater risk of developing CAP. Exposure to low levels of tobacco smoking or passive smoking has also been shown to be associated with modification in the lung cell biology similar to that seen in current smokers.[211,212]

A recent systematic review of risk factors for CAP in adults published by Almirall *et al*. found that tobacco smoking was a significant risk factor for CAP compared to never smokers, however the strength of association was not quantified.[26] Passive smoking has been shown to increase the risk of lower respiratory tract infections (LRTIs) in children whose parents smoke[213], yet there has been no systematic review to summarise the risk for developing CAP in adults.

The aim of this systematic review and meta-analyses was to summarise the available evidence regarding the effect of tobacco smoking and passive smoke exposure on the risk of developing CAP in adults, to determine the strength of the association and to examine whether there is a 'dose-response' association between amount of tobacco smoked and the risk of developing CAP.

6.2 Methods

This systematic review was conducted using a predefined protocol which was registered with PROSPERO database (CRD42018093943, Appendix 7) and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.

6.2.1 Search strategy and study selection

The search strategy was designed to find published studies. Comprehensive searches of the following biomedical electronic databases were conducted: MEDLINE, Embase, CINAHL, PsycINFO and Web of Science from the commencement of these databases to October 2017. The search strategy included subject headings and keywords related to "community acquired pneumonia" and "smoking". Search keywords were determined from the Cochrane review group terms for tobacco.[214] Details of the search strategy for each database are found in Appendix 8. The reference list of all included studies was screened for inclusion.

This review included observational studies; prospective and retrospective cohort studies and case-control studies. Cross-sectional studies were excluded. Studies published in all languages were considered and no date restrictions were placed on searches. Studies comprising adults aged 15 years and above with either a clinical or radiology-confirmed diagnosis of CAP were included. Studies comprising patients with hospital acquired pneumonia, aspiration pneumonia, active pulmonary TB and post-obstructive pneumonia secondary to thoracic malignancy were excluded.

Two authors (VB, AH, RM or TM) independently screened titles and abstracts using Covidence software[215] and subsequently reviewed full-texts of retrieved studies for eligibility. Disagreement was resolved by discussion and consensus, involving a third reviewer (TM or WSL) where necessary.

6.2.2 Data extraction and assessment of methodological quality

Two authors (VB, RM or TM) independently extracted all data for studies in English whilst data from non-English studies were extracted by a single reviewer (TL, LB, MOB or KN) who was literate in that particular language using a standardised form (Appendix 9). Any disagreements that arose between reviewers were resolved through discussion, or with a third reviewer (TM) when required. Information on study population, study design, exposure of interest (tobacco smoking) including different exposure categories (e.g. never, ever, ex-, current, 'not current' and passive smokers), outcome (CAP) and the adjusted/ unadjusted effect size (either odds ratios (ORs) or hazard ratios (HRs)) were collected.

Methodological quality was assessed using the Newcastle-Ottawa Quality Assessment Scale[216] for either cohort or case-control studies depending on individual study design. This scale is based on three broad categories; (1) selection of the study sample (four points), (2) comparability of the sample groups (two points) and (3) ascertainment of exposure/ outcome (three points). Thus, studies were scored out of a total of nine points. Scores were chosen *a priori* to indicate different levels of methodological quality (0-3: low quality, 4-6: moderate quality, 7-9: high quality)

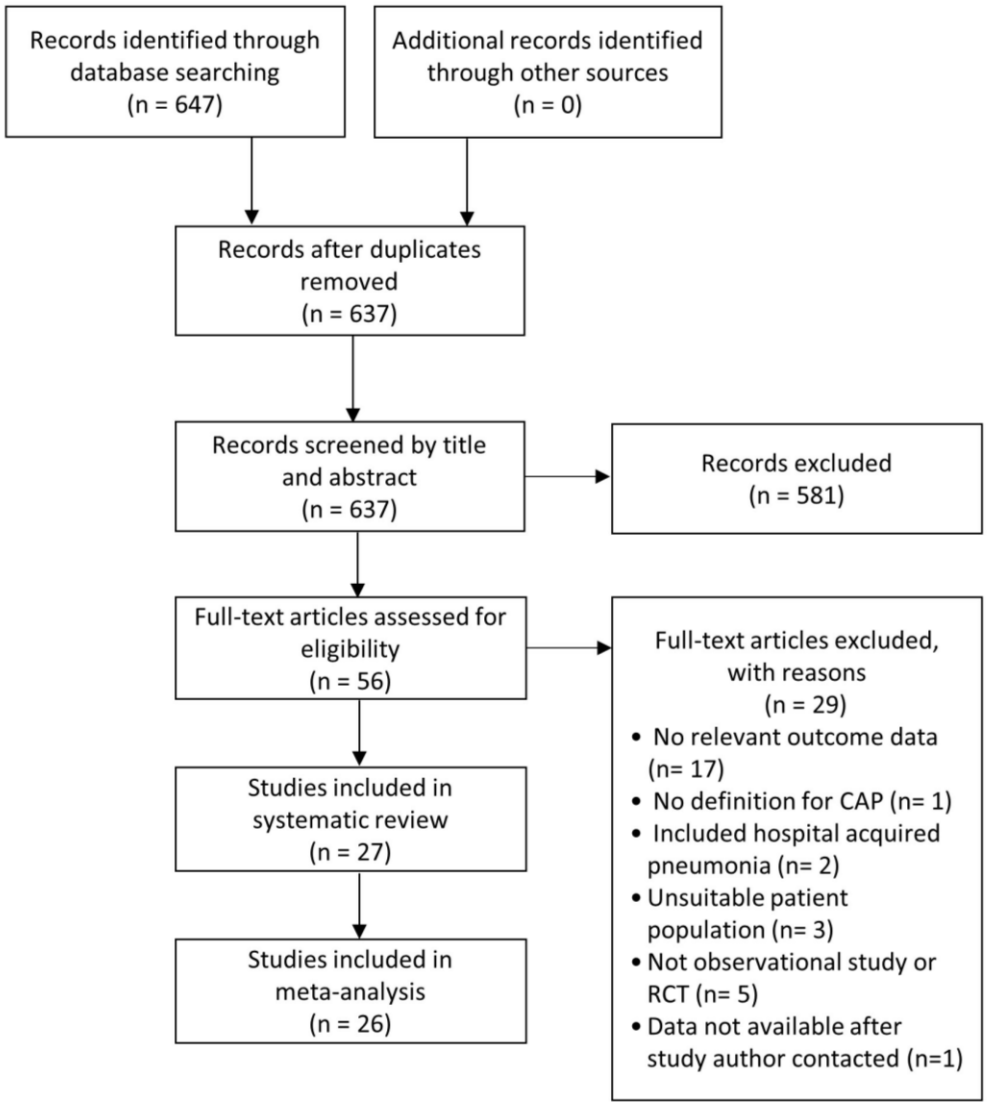
6.2.3 Data synthesis

We reviewed the extracted results to assess if adequate similarity existed for study outcomes to conduct a random-effects meta-analysis using Stata/ SE 15.1 (©StataCorp. 2017). Meta-analysis was performed using 26 studies comparing current (selecting the highest amount of tobacco smoked for current smokers where there was more than one category), ever, ex- and passive versus never smokers in addition to comparing current versus 'not current' smokers. We assessed publication bias visually using a funnel plot for the association between current smoking and the risk of CAP given that there were more than 10 studies included in this meta-analysis. We summarised studies with pooled ORs and HRs separately with 95% confidence intervals. Measures of effect adjusted for confounders (age and sex were *a priori* confounders) were used in preference to crude measures of effect. The I^2 statistic was used to assist with assessment of heterogeneity between studies. We performed sensitivity analysis excluding studies with only specific medical conditions (we use the term 'selected clinical populations' in the rest of this paper) so that the data would be representative of the general population. In order to explore ascertainment bias, we compared the effect size in primary care versus secondary care settings. We plotted the log ratio for each category within a study (assuming a linear relationship) and estimated the dose-response regression coefficient to determine the dose-response association between the dose of current smoking and the risk of developing CAP.

6.3 Results

The search strategy initially identified 647 studies, from which 56 full-text articles (including five non-English studies; French, Chinese, German and Spanish) were reviewed (**Fig 6-1**). Twenty-five English studies and two non-English studies were included in the systematic review (n=460,592 participants). The most common reason for exclusion was lack of documented relevant outcome data (n= 17/56).

Fig 6-1: PRISMA flow diagram for study selection



6.3.1 Characteristics of included studies

Of 27 included studies, there were 13 cohort studies and 14 case-control studies. All except two studies included both genders; two studies only included men.[217,218] Five studies had selected clinical populations including patients with human immunodeficiency virus (HIV)[219], selected HIV-related medical conditions[218], minor thoracic injury[220] and chronic obstructive pulmonary disease (COPD)[221,222]. One study reported an outbreak of Legionnaires' disease and included participants who visited an aquarium.[223] Six studies were conducted in primary care, nine in hospitals, four in mixed settings, six in community settings and two not specified (**Table 6-1**). The definition of CAP was based on radiological confirmation in 16 studies, diagnostic coding in five studies (four studies used ICD-9 codes and one study used Clinical Practice Research Datalink read codes) and clinical criteria in five studies; one study did not report the way CAP was defined.

Table 6-1: Characteristics of 27 included studies for systematic review; ordered by year, author.

First Author	Year	Study design	Country	Setting	Study population	Final study number	How is smoking status measured?	Smoking categories*	CAP definition
Case –control studies									
Almirall	1999	Multicentre prospective	Spain	Mixed	Mean age: men 56.1 (SD 19), women 51.1 (SD 20.7) Excluded a secondary concurrent disease or a noninfectious origin, HIV, active cancers, dementia.	Cases 205/ Controls 475	Questionnaire	Never Ever Ex Current	Acute lower respiratory tract infections for which antibiotics were prescribed, associated or not with new focal signs on examination of the chest and radiographic infiltrate indicative of pneumonia.
Almirall	1999	Multicentre retrospective	Spain	Mixed	Mean age: men 56.1 (SD 19), women 51.1 (SD 20.7) Male: 54.6% Excluded HIV, active cancer, aspiration, active lung TB, nursing homes residents, HAP, dementia, non-contactable.	Cases 205/ Controls 475	Questionnaire completed by nurses/ doctors	Never Ex Current	Acute lower respiratory tract infections for which antibiotics were prescribed, associated or not with new focal signs on examination of the chest and radiographic infiltrate indicative of pneumonia

Farr	2000	Multicentre prospective	UK	Primary care	Mean age: cases 54, controls 44 Male: cases 55%, controls 45%	Cases 66, Controls 489	Questionnaire	Never ‡ Ex Current Passive	Acute lower respiratory tract infection for which an antibiotic was prescribed associated with new focal signs on chest examination and new radiographic pulmonary shadowing.
Farr	2000	Multicentre prospective	England	Hospital	Age: cases 44.9, controls 26.5% ≥60 Male: cases 60.7%, controls 54.3% Excluded if CAP was not the main reason for admission, expected terminal event, distal to a bronchial event, pulmonary TB, control had CAP as an adult.	Cases 178, Controls 385	Questionnaire	Never Current (mild, heavy) Passive	Acute respiratory illness with radiological pulmonary shadowing which was at least segmental or present in more than one lobe.Two control subjects for each case were selected at random from the electoral registers for the main catchment areas of the hospitals where the cases were treated.
Piednoir	2003	Single centre retrospective	France	Hospital	Mean age: 88.3 (SD 4.1) Male: 68%	Cases 101, Controls 101	Medical records	Not current Current	Radiological diagnosis of one or more opacities + one of the below: bacterial infection, temp > 38,

					Excluded if not confirmed radiologically.				legionella, cough, wheeze, breathing difficulty
§ Greig	2004	Single centre retrospective	Australia	Community	Median age: 64 Male: 57% Included participants who visited an aquarium. Controls excluded if had clinical disgnosis of CAP	Cases 104, Controls 201	Telephone interview using standardised questionnaire	Never Current	Fever, cough, pneumonia in the 2/52 after a visit to Melbourne Aquarium/ close vicinity + confirmed by ≥ one test: (1) +ve urinary antigen test (2) ≥ 4x (to ≥ 128) rise in antibody titre against L pneumophila between paired acute and convalescent phased sera (3) Isolation of Legionella spp. from resp secretions (4) stable high (>512) titre in convalescent serum
Bai	2007	Single centre retrospective	China	Hospital	Age: cases 76.90, controls 74.64 Male: 75%	Cases 128, Controls 306	Questionnaire completed by patients	Current Ever	Not reported
Almirall	2008	Multicentre prospective	Spain	Primary care	Cases: mean age: 54.6 (SD 20.7) (women) – 58.6 (SD 19.8) (men) Male: 52.9% Controls: Mean age : Controls	Cases 1336/ Controls 1326	Questionnaire	Never Ex Current Passive	Acute lower respiratory tract infection for which antibiotics had been prescribed, with the appearance of previously unrecorded focal signs on physical examination of the chest and new radiological findings suggestive of pneumonia infiltrate.

					54.6 (SD 20.6) (women)– 58.9 (SD 19.6) (men) Male: 52.6% Excluded aspiration, active pulmonary TB, HAP, nursing homes residents.				
Jackson	2008	Multicentre retrospective	USA	Mixed	Age: 65-94 Male: 51% Excluded nursing home/ hospice care residents, if they had <2 visits to Group Health providers in previous 2 years.	Cases 1173, Controls 2346	Medical records	Never Ever	ICD-9 codes for CAP; These episodes were then validated either by review of electronically available reports of chest radiographs obtained within 30 days before or after the visit or, for events in the hospital, by review of the hospital records.
Tas	2008	Single centre retrospective	Turkey	Hospital	Mean age: cases 22.18 (SD 1.22), controls 22.18 (SD 1.23) Male: 100% Excluded ex-smokers, soldiers with chronic diseases	Cases 58, Controls 580	Interview	Never Current	Patients with clinical, laboratory and radiological findings compatible with pneumonia were hospitalized

Loeb	2009	Multicentre retrospective	Canada	Hospital	Mean age: cases 79.1 (SD 7.6),controls 74.4 (SD 6.7) Male: cases 60.4%, controls 31.5% Excluded nursing home residents, infection at another site (in addition to CAP) at the time of enrolment, and residence outside the study catchment areas. Control participants were excluded if they had been diagnosed with CAP in the previous 12 months or had any other active infection.	Cases 717, Controls 867	Questionnaire completed by interviewer	Ever Passive	≥ 2 of the following symptoms and signs: temperature higher than 38.1C, productive cough, chest pain, shortness of breath, or crackles on auscultation, new opacity on a chest radiograph interpreted by a radiologist as being compatible with pneumonia.
Gau	2010	Single centre retrospective	USA	Hospital	Mean age: cases 80.3 (SD 8.5)/, controls 79.8 (8.1) Male: cases 39%, controls 33% Excluded aspiration,	Cases 194, Controls 952	Medical records/ standardised form	Never ‡ Ex Current	Discharge diagnosis and further confirmed by the report of the radiographic findings (a new infiltrate or consolidation) suggestive of pneumonia.

					active lung cancer/ metastatic disease, ventilator-associated/ HAP, death as inpatient, haemodialysis patients, incomplete records, patients who could not recall medication use				
Teepe	2010	Multicentre prospective	Dutch	Primary care	Age: cases 34.3, controls 32.1 Male: cases 39.1%, controls 35.5%	Cases 156, Controls 468	Questionnaire completed by trained research nurse at interview	Not current Current	International Classification of Primary Care (ICPC) code R81:Either a confirmation by radiography or the presence of ≥ 3 of the following signs/ symptoms: decreased intensity of breath sounds, dullness on chest percussion, inspiratory crackles, increased vocal resonance, fever, local chest pain on deep inhalation
Almirall	2014	Multicentre prospective	Spain	Primary care	Median age: cases 65 (14-96), controls 63 (15-100) Male: cases 25%,	Cases 471/ Controls 532	Questionnaire completed by trained physician/	Never; passive Never; non-	Acute lower respiratory tract infection for which antibiotics had been prescribed with appearance of new or previously unknown

					controls 29% Excluded aspiration, HAP, active lung TB, if another non-infectious respiratory disease was later confirmed.		nurse at interview	passive	focal signs on physical examination and radiography of the chest
Cohort studies									
§ Conley	1996	Multicentre prospective & retrospective	USA	Not specified	Median age: 36-38 Male: 100% Included HIV infected men Excluded ex-smokers and intermittent smokers.	232	Questionnaire	Never Current	Illness must be severe enough to require a visit to a physician, a diagnosis of 'pneumonia' by the clinician and his prescription of an antibiotic.
Baik	2000	Multicentre prospective	USA	Community	Age: men 44-79, women 27 -44 Excluded HAP, diagnosis of pneumonia not identified by medical records or by supplemental	104491	Questionnaire	Never Ex Current	First documented physician diagnosed CAP Men: CXR infiltrate documented in the report Women: self-report

					questionnaire, CAP before the beginning of the study, those who didn't respond to questions on body weight and physical activity, women with probable or possible CAP.				
Jackson	2004	Multicentre prospective	USA	Mixed	Age: 53% 65- 74, 38% 75 - 84 Male: 42% Excluded HAP	Hospitalised 1266 OPD 1881	Outpatient visit documentation for GHC	Not current Current	For CAP that required hospitalisation: Treating physician considered CAP as the aetiology For outpatient CAP: ICD 9 codes, chart review indicated that pneumonia was the most likely diagnosis, CXR within 14 days of visit, & if the patient had not been hospitalized in the prior 7 days.

O-Meara	2005	Multicentre prospective	USA	Community	Mean age: Hospitalised 75, Not hospitalised 72.6 Male: hospitalised 49%, not hospitalised 42% Excluded institutionalised, not ambulatory at home, under hospice care, receiving radiation or chemotherapy for cancer, not expected to remain in the area for ≥ 3 years, unable to be interviewed	5888	Interview	Never ‡ Current Ever	Pneumonia identified by codes assigned to hospital discharge diagnoses according to ICD-9 codes (481, 482, 486)
§ Gordin	2008	Multicentre prospective	33 countries	Not specified	Median age: 43 Male: 72.8% Included HIV infected persons	5472	Standardised case report by trained interviewer	Never Ex Current	(1) ‘‘confirmed’’: compatible clinical and radiographic evidence with histologic or microbiologic support (2) ‘‘probable’’: signs and symptoms of pneumonia with compatible radiographic abnormalities

§ Mannino	2009	Multicentre prospective	USA	Community	Age ≥ 45 Male: 44.5%	214	Questionnaire	Never Ex Current	Hospitalisations that include pneumonia discharge code (ICD-9 codes 480 - 486) within 36 months
§ Chauny	2012	Multicentre prospective	Canada	Hospital	Mean age: 53 (SD 17) Male: 63% Included patients with minor thoracic injury Excluded spontaneous rib fracture not associated with trauma, confirmed diagnosis of hemothorax, pneumothorax, lung contusion, or any other significant internal thoracic or abdominal injury at their initial ED visit, if they could not be followed as	1057	Questionnaire completed by patients	Never Ex Current	Presence of pneumonia on radiologic reports, with compatible patient complaints and physical examination in the first 2 weeks, or the reported diagnosis of delayed pneumonia, with antibiotic administration.

					outpatients, or if the interval from time of injury to ED visit exceeded 3 days.				
Takahashi	2013	Single centre prospective	Vietnam	Hospital	Median age: 50 Male: 52% Excluded HAP, no interpretable CXR.	174	Standardised form	Never Ever	Hospitalised with ≥ 2 of the following: (1) fever and/or cough (2) fast and/or difficulty of breathing (3) any additional severe symptoms including respiratory rate over 30 per minute, SpO2 under 90%, systolic blood pressure under 90 mmHg, pulse rate more than 130/min, white blood cell count over 20,000 or under 4,000 cells/µL, CRP over 20 mg/dl, dehydrated, altered consciousness and other worse general status. A senior pulmonologist and two physicians interpreted all chest X-ray films independently. A case

									was categorised as CAP if ≥ 2 evaluators agreed on the presence of consolidation.
Yende	2013	Multicentre prospective	USA	Community	Mean age: 59.23 (SD 10.06) Male: 44.1% Excluded: CHS: wheelchair bound, unable to participate in the examination at the field centre, definitive plans to leave the area, active cancer. Health ABC: recent treatment of cancer, severe dementia, plans of leaving the area within 3 years.	16260	Self-report	Never Ex Current	ICD 9 code 480 - 487

§ Attia	2015	Multicentre prospective	USA	Hospital	Median age: 44-50 Male: 98% Included HIV infected veterans	41993	Electronic health record/ Veterans Affair database	Never Ex Current	Inpatient ICD-9 code for CAP
Breitling	2016	Multicentre prospective	Germany	Primary care	Age: 50-75 Male: 44.6%	9419	Questionnaire	Never Ex Current	First episode of pneumonia reported either by the participants or their physicians
Jackson	2016	Multicentre prospective	USA	Community	Age ≥65 Male: 41%	3375	Questionnaire completed by interviewer	Never Ex Current	(ICD-9-CM) codes 480–487.0 or 507.0 assigned to outpatient and inpatient medical encounters. • Presumptive pneumonia episodes were considered validated if manual review of chest radiograph reports within 30 days of first pneumonia diagnosis indicated the presence of an infiltrate not known to be chronic. • If no CXR, validated by reviewing hospital admission, consultation, and discharge

									summaries.
§ Braeken	2017	Multicentre retrospective	UK	Primary care	Mean age: 67 Male: 55.2% Included patients with COPD Excluded asthma, pneumonia in preceding 3 months, pulmonary TB and unknown smoking status.	254 275	CPRD database	Never Ex Current	Physician-recorded pneumonia diagnosis, identified by read codes.

Abbreviations

SD: standard deviation, HIV: human immunodeficiency virus, TB: tuberculosis, HAP: hospital acquired pneumonia, ED: emergency department, ICD: International Classification of Diseases, COPD: chronic obstructive lung disease, CHS: Cardiovascular Health Study, Health ABC: Health, Aging, and Body Composition

Legend

* Smoking categories have been renamed from original studies in this table to match Table 1 for consistency: never and non-smokers in the 'never' category; lifetime smoking history of > 100 cigarettes, 'current/ past' and 'current/ex-' in the 'ever' category, ex-, former and past smokers in the 'ex' category; and current and active smokers in the 'current' category.

‡Studies which had information for ‘never’ smoking category although did not explicitly state the category.
§ Studies which had selected clinical population

6.3.2 Risk of bias

Most of the studies (n=16 studies) included were of moderate quality with a median quality score of six (IQR 6-7) (**Table 6-2**). Using the a priori methodological quality scores, we judged ten studies to be of high quality and one study of low quality. Twenty-four studies (88.9%) had clear definitions of CAP either using independent blind assessment of chest radiographs, medical records or record linkage (e.g. ICD codes) and 23 studies (85.2%) adjusted for confounders. Thirteen (92.9%) out of all case-control studies scored low as a result of lack of non-response rate reporting and poor smoking status ascertainment (obtained information from interview that was not blinded to case/ control status or were self-reported). In contrast, over half of the cohort studies (n=8 studies, 61.5%) scored well for smoking status ascertainment; either from a secure medical record or structured interview with the participant. The quality for some of the cohort studies dropped due to a combination of lacking a truly representative exposed cohort (n=8 studies, 61.5%), not demonstrating that CAP was not present at the start of the study (n=8 studies, 61.5%) and not having a statement about loss to follow-up (n=9 studies, 69.2%).

Table 6-2: Risk of bias for included studies (using Newcastle Ottawa Scale)

First Author	Year	Study quality			
		Selection (max= 4)	Comparability (max= 2)	Outcome (max= 3)	Total
Almirall	1999	4	2	1	7
Almirall	1999	4	2	1	7
Almirall	2008	4	2	1	7
Almirall	2014	4	1	1	6
Attia	2015	2	2	2	6
Bai	2007	2	2	0	4
Baik (men)	2000	2	2	3	7
Baik (women)	2000	2	2	2	6
Braeken	2017	4	2	2	8

Breitling	2016	2	2	2	6
Chauny	2012	1	0	1	2
Conley	1996	2	2	2	6
Farr	2000	4	2	2	8
Farr	2000	4	2	1	7
Gau	2010	3	2	2	7
Gordin	2008	2	2	1	5
Greig	2004	3	2	1	6
Jackson	2004	2	2	2	6
Jackson	2008	3	1	2	6
Jackson	2016	3	2	2	7
Loeb	2009	4	2	1	7
Mannino	2009	1	2	3	6
O-Meara	2005	2	2	2	6
Piednoir	2003	2	2	1	5
Takahashi	2013	1	2	1	4
Tas	2008	4	1	1	6
Teepe	2010	3	2	1	6
Yende	2013	2	2	2	6

6.3.3 Smoking status

The most commonly used definitions of smoking status are detailed in Table 6-3. Most studies state the smoking categories without providing detailed definition for respective categories; we have used the definition for each category from the Glossary detailed in the Adult Tobacco Use Information by the Centres for Disease Control and Prevention (Table 6-3).[224]

Table 6-3: Smoking categories used in included studies

Smoking categories	Definition[224]	Synonyms used in included studies	Number of studies
Never	Never smoked or lifetime smoking history of <100 cigarettes	Non	27
Ever	Lifetime smoking history of ≥100 cigarettes	'Current/ past' 'Current/ ex'	4
Ex	Lifetime smoking history of ≥100 cigarettes and stopped smoking at the time of the study	Former, past	15

Current	Lifetime smoking history of ≥100 cigarettes and currently smokes at the time of the study	Active	18
Passive	Never smokers who are exposed to environmental cigarette smoke	Exposure to second-hand smoke	6

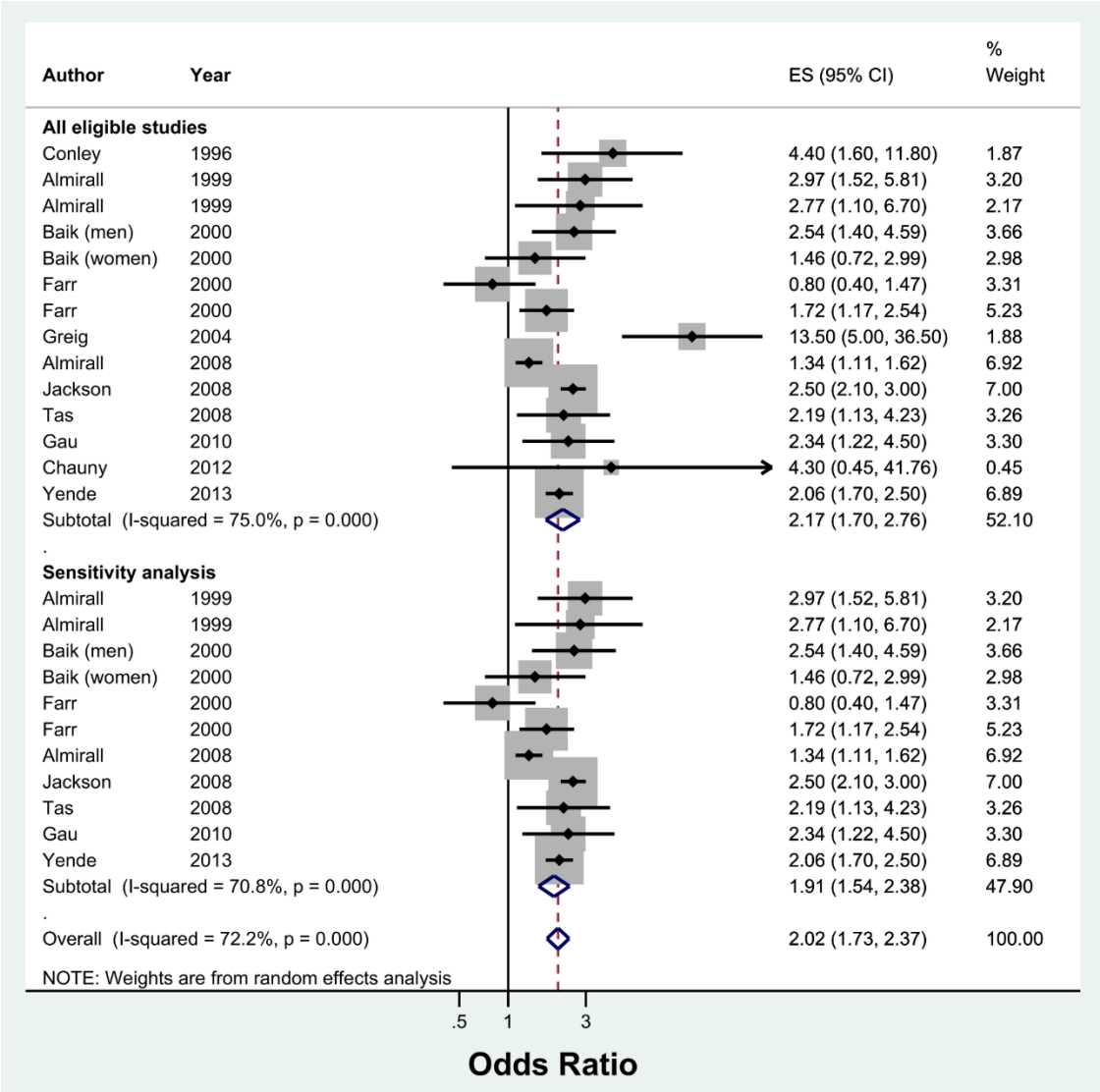
Four studies quantified tobacco smoking by documenting pack-years[225,226] and reporting qualitative descriptions from light through to heavy smoking.[218,227] 'Not current' smoking category which could include never, ever and ex-smokers was used in two studies. The proportion of current smokers with CAP was higher in secondary care (31-79%) compared to primary care (21-27.3%).

6.3.4 Meta-analyses

Meta-analysis of 13 studies showed that current smokers were more than twice at risk of developing CAP than never smokers (pooled OR 2.17, 95% CI 1.70-2.76, I^2=75%) (**Fig 6-2**). Sensitivity analysis excluding studies which were not representative of the general population (two studies with selected clinical populations[218,220] and one study which recruited participants who visited an aquarium[223]) found a marginally lower effect (pooled OR 1.91, 95% CI 1.54–2.38, I^2=70.8%, n=10 studies) (**Fig 6-2**). There was no evidence of publication bias identified from the funnel plot for the association between current smoking and the risk of CAP (**Fig 6-3**). Studies that reported hazards ratios found that current smokers were 53% more likely to develop CAP than never smokers (pooled HR 1.52, 95% CI 1.13-2.04, I^2=89.5%, n=7 studies) (**Fig 6-4**). The risk increased slightly when three studies with selected clinical populations were removed (pooled HR 1.72, 95% CI 1.43-2.07, I^2=19.3%) (**Fig 6-4**). Compared to 'not current' smokers, meta-analysis of two studies revealed that current smokers were almost three times at risk of developing CAP (pooled OR 2.75, 95% CI 1.29-5.88, I^2=58.3%, n=2 studies) (**Fig 6-5**). There was only one study which compared current smokers to 'not current' smokers and

reported hazards ratio (HR 1.31, 95% CI 1.17-1.46), hence this study was not included in the meta-analysis. [228] Meta-analysis of four studies showed that ever smokers were more than twice at risk of developing CAP than never smokers (pooled OR 2.31, 95% CI 1.99-2.69, I^2=0%, n=4 studies) (**Fig 6-6**).

Fig 6-2: Meta-analysis of risk of community acquired pneumonia in current smokers relative to never smokers (Odds Ratio).



Study by Baik *et al.* had relevant data subdivided by gender, therefore data from this study were included as two separate entities (i.e. men and women).

For Fig 6-2, Fig 6-4 - Fig 6-8:

Grey box = effect estimates from single studies. Diamond = pooled result with confidence interval. Vertical line at '1' on the x-axis is the line of no effect. Weight (in %) = influence an individual study had on the pooled result.

Fig 6-3: Funnel plot for the association between current smoking and the risk of developing CAP

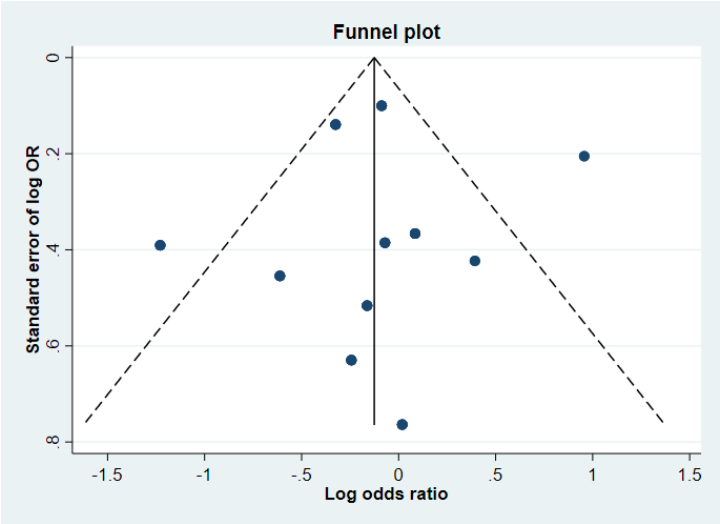


Fig 6-4: Meta-analysis of incidence of community acquired pneumonia in current smokers relative to never smokers (Hazards Ratio)

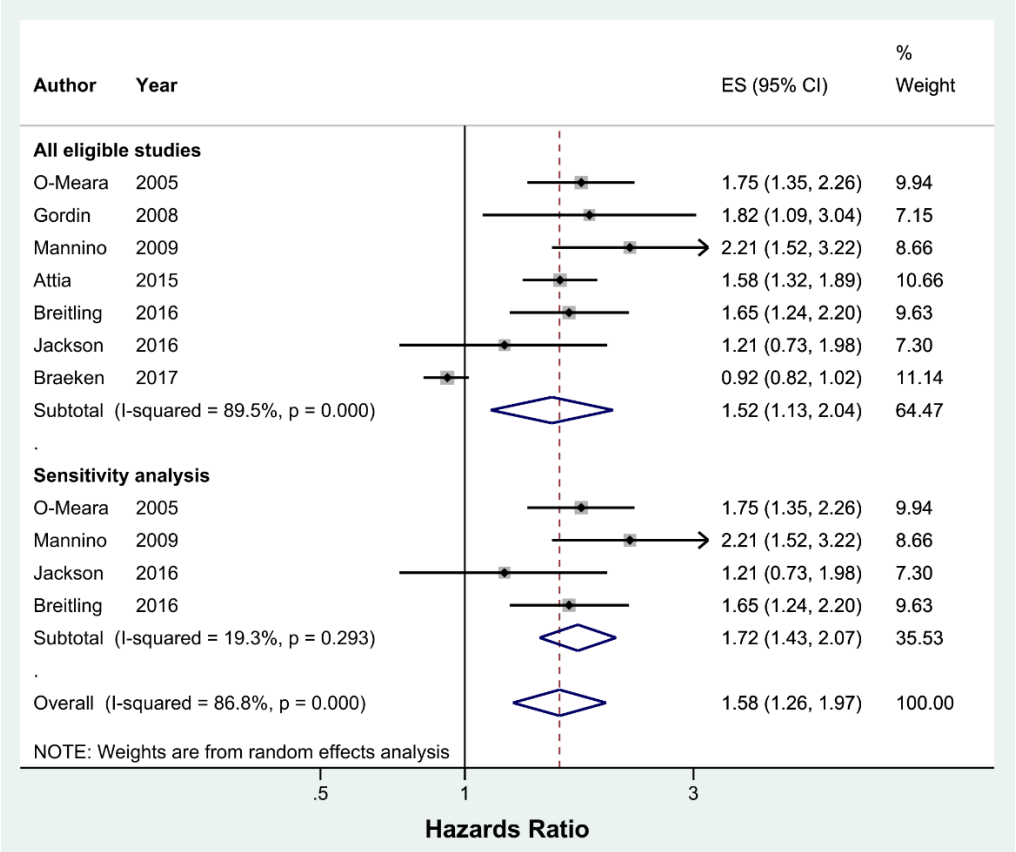


Fig 6-5: Meta-analysis of risk of community acquired pneumonia in current smokers relative to 'not current' smokers (Odds Ratio)

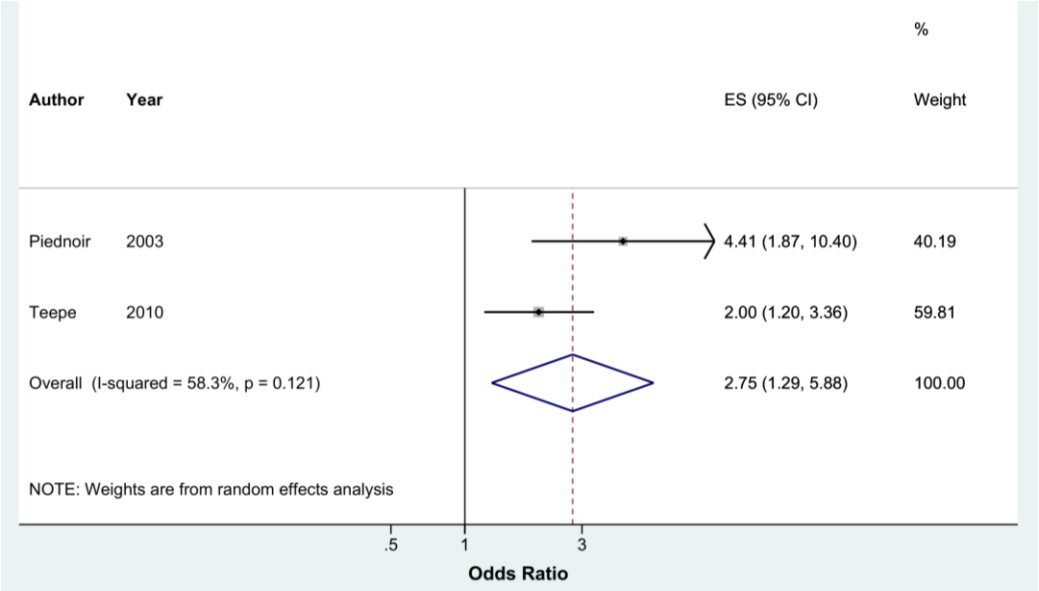
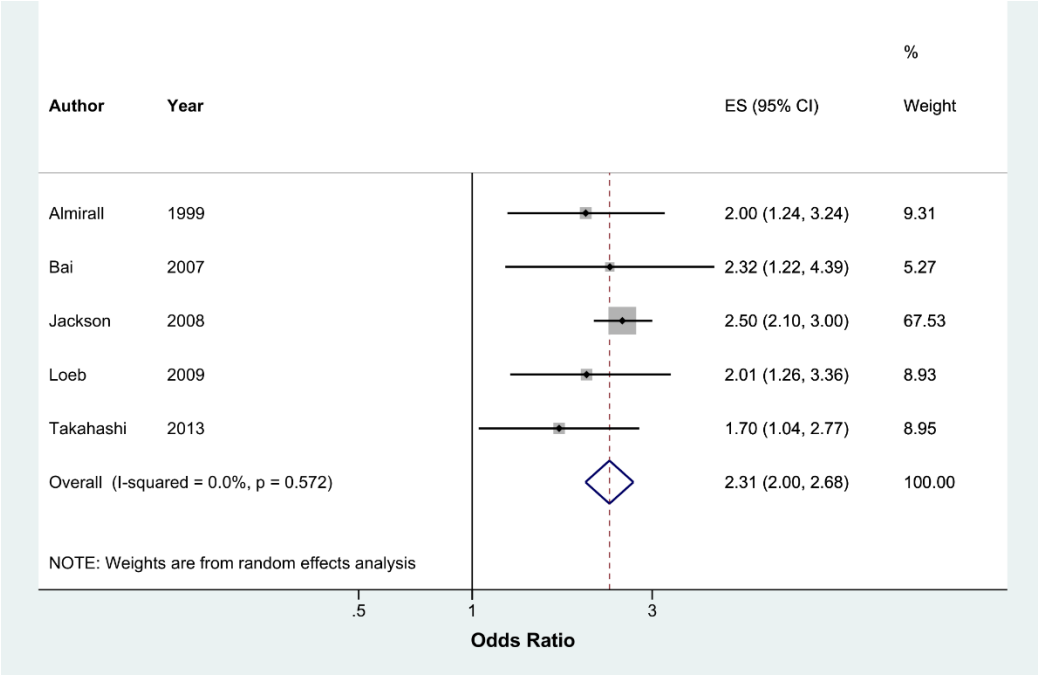


Fig 6-6: Meta-analysis of risk of community acquired pneumonia in current smokers relative to 'ever' smokers (Odds Ratio)



Ex-smokers were 49% more likely to develop CAP than never smokers (pooled OR 1.49, 95% CI 1.26-1.75, I^2=13.3%, n=8 studies) (**Fig 6-7**). Sensitivity analysis excluding two studies which were not representative of the general population found a similar result (pooled OR 1.51, 95% CI 1.24-1.84, I^2=29.9%, n=6 studies). Studies reporting hazard ratios had a high level of heterogeneity and did not find a significant effect between ex-smokers and the risk of developing CAP (All eligible studies: pooled HR 1.18, 95% CI 0.91-1.52, I^2=85.4%, n=6 studies and sensitivity analysis: pooled HR 1.25, 95% CI 0.88-1.78, I^2=75.3%, n=2 studies) (**Fig 6-8**).

Fig 6-7: Meta-analysis of risk of community acquired pneumonia in ex-smokers relative to never smokers (Odds Ratio)

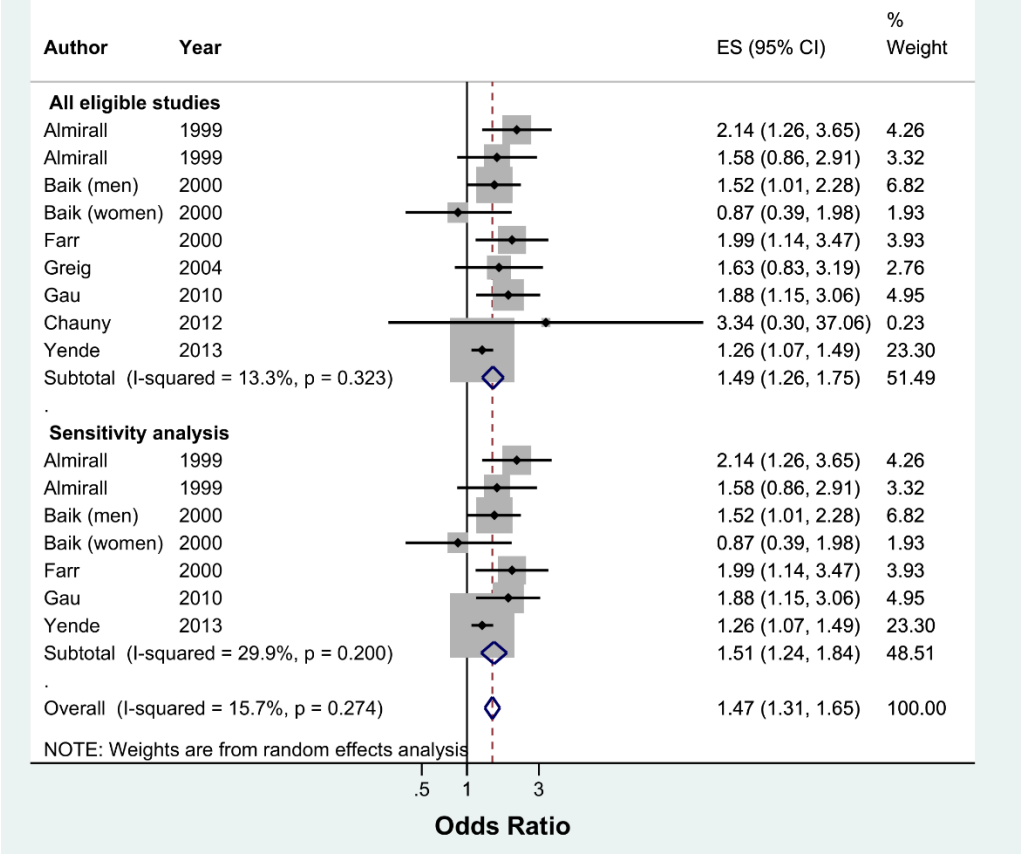
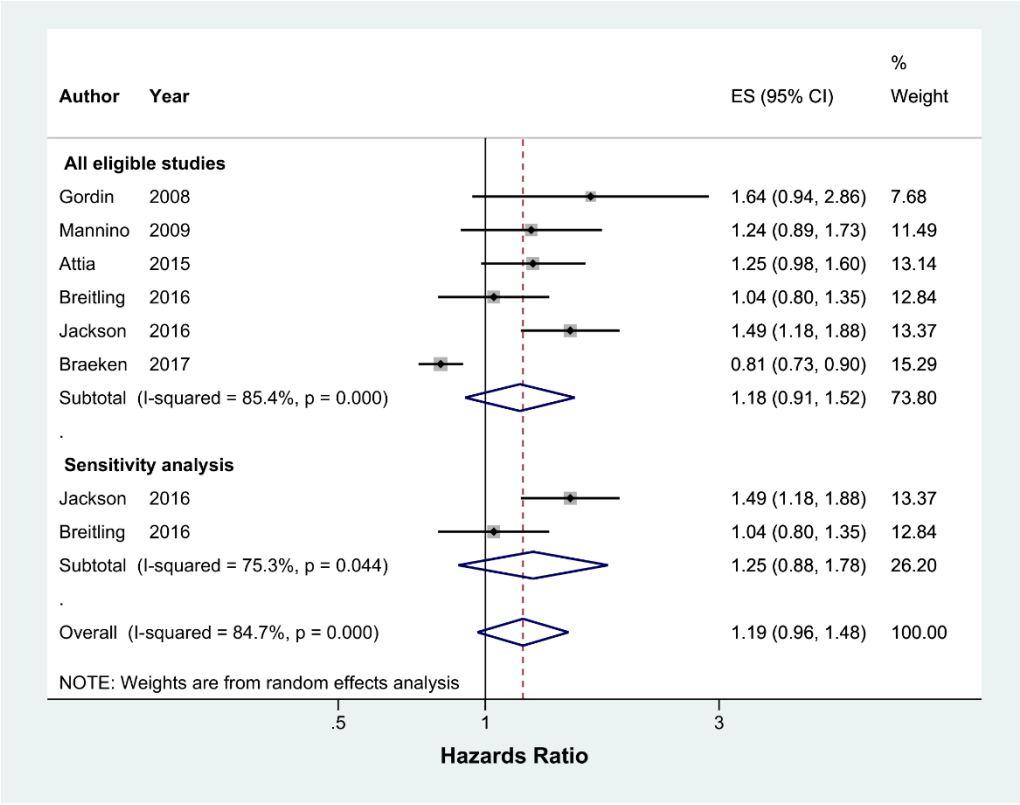


Fig 6-8: Meta-analysis of incidence of community acquired pneumonia in ex-smokers relative to never smokers (Hazards Ratio)



For studies conducted only within a primary care setting, the effect of current smoking on the risk of developing CAP was not statistically significant (pooled OR 1.14, 95% CI 0.72-1.82, I^2=55.1%, n=2 studies and pooled HR 1.21, 95% CI 0.68-2.15, I^2=92.8%, n=2 studies) whereas for studies conducted in a secondary care setting, current smoking was significantly associated with CAP compared to never smokers (pooled OR 1.95, 95% CI 1.45- 2.62, I^2=0.0%, n=4 studies and HR 1.58, 95% CI 1.32-1.89, n=1 study).

Passive smoking was associated with a 13% increased risk of developing CAP compared to those who were not exposed to passive smoking, however this result was not statistically significant (pooled OR 1.13, 95% CI 0.94-1.36, I^2=26.8%, n=5 studies). In a sensitivity analysis of those ≥ 65 years old, passive smoking was associated with 64% increased risk of CAP (pooled OR 1.64; 95% CI 1.17-2.30, I^2=0%, n=2 studies).

6.3.5 Dose-response trend: narrative review

Five studies had information on the dose-response association between amount of smoking and the risk of developing CAP. We performed dose-response analyses using the data arising from these five studies (**Table 6-4**) although a meta-analysis was not possible due to variations in the method of quantification of smoking exposure across studies. Significant dose-response relationships were found in all studies; there were two linear[225,229] and three non-linear[218,227,230] associations with the effect in one study being mainly driven by results from the highest two categories (**Table 6-4**).[227]

Table 6-4: Dose-response relationship between amount of smoking and risk of developing CAP. Trend (OR)* of 1.xy means xy% increase of risk of CAP per increase in category documented in the 'Quantification of smoking exposure' column.

Study	Smoking status	Quantification of smoking exposure	Trend (OR)*	p value	Association
Almirall 1999	Current & ex-smokers	Pack-years • 0 • 5-16.4 • 16.5-38 • >38	1.37, 95% CI 1.17-1.61	<0.001	Linear
Almirall 2008	Current & ex-smokers	Packs of cigarettes smoked daily x 365 x years smoked[$] • 0 • 1-150 • 151-300 • >300	1.27, 95% CI 1.17- 1.38	<0.001	Linear
Almirall 1999	Current smokers	Cigarettes smoked daily • 0 • 1-9 • 10-20 • >20	1.30, 95% CI 1.02-1.67	0.037	Non-linear
Farr 2000	Current smokers	Cigarettes smoked daily x years smoked • 0 • 1-225 • **226-578** • **579+**	1.52, 95% CI 1.30- 1.78	<0.001	Non-linear; effect mainly in the highest two categories of smoking **(in bold)**

Conley 1996	Current smokers	Packets of cigarettes daily • ≤ half ('light') • half to <2 ('moderate') • >2 ('heavy')	1.51, 95% CI 1.10-2.08	0.011	Non-linear

[$]This formula was clarified directly by personal correspondence with study author.

6.4 Discussion

This study quantified the effect of tobacco smoking on the risk of developing CAP through a meta-analysis. Our study revealed robust evidence that current and ex-smokers are significantly at higher risk of developing CAP whilst passive tobacco smoke exposure had a significant effect only in those aged ≥ 65. The strongest associations were evident in studies conducted in secondary care. In addition, a dose-response trend with higher risk of CAP amongst current smokers who smoke higher amounts of tobacco was noted.

Current smoking has been associated with a wide spectrum of infectious diseases including bacterial pathogens (Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Staphylococcus aureus, Legionella pneumophila, Mycobacterium tuberculosis) and viral pathogens (influenza, rhinovirus, HIV).[231–236] Whether smoking increases the risk of infection from different respiratory pathogens by the same degree could not been fully examined in this systematic review due to lack of relevant data in the included studies.

We quantified the risk of developing CAP in current smokers to be similar to the association of smoking with asthma (RR 1.61; 95% CI, 1.07-2.42), idiopathic pulmonary fibrosis (OR 1.58; 95% CI 1.27-1.97), obstructive sleep apnoea (RR 1.97; 95% CI 1.02 – 3.82), stroke (HR 1.58; 95% CI 1.40-1.78) and acute coronary syndrome (HR 1.98; 95% CI

1.75-2.25) though lower than that of developing lung cancer (HR 13.1; 95% CI 9.90-17.3) and COPD (RR 4.01; 95% CI, 3.18-5.05).[237–240]

Our findings advance the descriptive presentation in two previous systematic reviews which reported that smoking is an independent modifiable risk factor for developing CAP alongside other lifestyle factors including alcohol abuse, low body mass index, having regular contact with children and poor dental hygiene.[26,241] Smoking also has an indirect effect on the risk of CAP as it is associated with COPD and poor dental health which are themselves independent risk factors for developing CAP. [226,230,237,242,243] This indirect effect has not been quantified.

In a cohort of immunocompetent adults aged 18-64 years old with invasive pneumococcal disease (IPD), Nuorti *et al.* showed that passive smoking was an independent risk factor (OR 2.5; 95% CI 1.2-5.1) with increased risk observed with longer duration of passive smoke exposure.[244] Although passive smoking was not associated with increased risk of CAP in adults of all ages, it is noteworthy that meta-analysis of two studies showed an increased risk in those ≥65 years; one study recruited patients from primary care (exposed to passive smoke at home) and the other following hospitalisation for CAP (exposed to any passive smoke). A combination of host factors such as comorbidities that accompany advanced age, polypharmacy and immune senescence as well as social factors including poor nutrition and crowding or long-term residential care may contribute to the increased risk of infection seen in the elderly. [245]

We were able to perform dose-response analyses using data from five studies. Our analyses confirmed that higher levels of smoking exposure are associated with higher risks of developing CAP. This is consistent with data from IPD where a linear dose-response relationship with number of cigarettes smoked daily has been reported.[246] In

the two studies that combined current and ex-smokers in their analyses, the dose-response relationship between amount of smoking and risk of CAP was linear, whereas in the remaining three studies which had current smokers, the relationship was non-linear. An individual patient data analysis would be required to determine how the differences in the categorisation of smoking status influence the linearity of the dose-response relationship.

6.4.1 Tobacco smoking and infection: immune mechanisms

In addition to structural mechanisms mentioned in the 'Introduction' section,[209,210,247] smoking may increase the risk of systemic infections by causing changes in cellular and humoral immune system function.[248] Smoking impairs polymorphonuclear leukocyte function which plays a significant role in the host defence against bacterial infection (depressed neutrophil migration and leukocyte chemotaxis),[249,250] decreases $CD4^+$ T cell counts which results in reduction of B cells that secrete antibodies (thus lowering serum immunoglobulin levels by approximately 10%),[251–255] increases $CD8^+$ T cell counts,[256] and decreases secretion of pro-inflammatory cytokines such as IL-1 and IL-6.[257,258] Nicotine from tobacco smoking can also suppress natural killer (NK) cell activity; NK cells are usually activated as part of the early immune surveillance response against viral infections.[259]

6.4.2 Effect of tobacco smoking cessation

The only study included in this review that reported time from smoking cessation to development of CAP was a population-based case-control study by Almirall *et al*. which reported that the risk of CAP reduced by 50% (OR) after five years of smoking cessation.[225] In a study of invasive pneumococcal disease (IPD), the risk of IPD in ex-

smokers reduced by 14% annually and to that of never smokers about 13 years after smoking cessation.[246] These observations alongside the results from this meta-analysis support the notion that ex-smokers have a lower risk of CAP than current smokers and that this risk decreases with duration of smoking cessation.

Why ex-smokers remain at risk of CAP is unclear. Bacterial adherence is crucial in the pathogenesis of infection. Ex-smokers have been shown to have increased in vitro adherence of *Streptococcus pneumoniae* to buccal epithelial cells for up to three years after smoking cessation which may contribute to the increased risk of CAP.[247] In terms of alterations to immune function, reports have been mixed; one study found a significantly lower proportion of NK cells in ex-smokers who had stopped smoking for over 20 years compared to never smokers (mean duration since smoking cessation of 10.7 years)[260] , whereas in another study of 10 ex-smokers where duration since smoking cessation ranged from six weeks to 10 years (mean= 4 years), NK cell activity was comparable to that of never smokers.[261] In heavy smokers (≥50 pack-years), smoking cessation for six weeks has been associated with a return of the CD4/ CD8 ratio to normal.[262], Therefore, although some of the immune related effects of smoking may be relatively rapidly reversed upon stopping smoking, other effects may be more prolonged, or possibly irreversible.

6.4.3 Strengths and limitations

This review comprehensively summarises the current body of knowledge regarding the effect of tobacco smoking on the risk of developing CAP and was reported in accordance with PRISMA checklist. Eligibility criteria were strictly applied to ensure identified studies only included patients with CAP, hence excluding hospital-acquired pneumonia, aspiration pneumonia, active pulmonary TB and post-obstructive pneumonia secondary

to thoracic malignancy. Overall, included studies were of moderate quality and no language restrictions were applied. The statistical heterogeneity for the meta-analysis varied across the different analysis, ranging from low (<25%) to high (>75%) level and did not change significantly in the sensitivity analysis.

An important limitation was the various ways in which smoking status was defined and smoking 'dose' quantified. For instance, the lack of distinction of 'ever' and 'not current' smokers from 'ex-smokers' precluded seven studies from the meta-analysis involving ex-smokers. Definitions of CAP also varied, though to a lesser extent. Studies that did not adopt the 'gold standard' of radiologically confirmed CAP (n=10 studies) may have captured some cases of LRTI or acute bronchitis instead. Non-pneumonic respiratory tract infections (RTIs) are generally considered to be more likely to be caused by viral pathogens instead of bacterial pathogens.[263] However, there are no comparative data to suggest a differential effect of smoking on the occurrence of viral versus bacterial RTIs. Therefore, inclusion of these studies is not expected to exert a major bias on pooled results.

6.4.4 Implications

This review provides good evidence to support recommendations for smoking cessation as well as avoidance of passive exposure to tobacco smoke, particularly in persons at high risk of developing pneumonia. Patients who recover from an episode of CAP are recognised to be at risk of recurrent CAP[57,264,265]. Therefore hospitalisation with CAP provides a valuable 'teachable moment' when smoking cessation should be promoted.[266–268]

Further research is warranted to establish why and for how long ex-smokers continue to be at higher risk of developing CAP following smoking cessation, compared to those who have never smoked. For future studies, a more standardised approach to reporting pack-years of smoking instead of qualitative descriptions with variable definitions would facilitate comparisons and synthesis of data.

Chapter 7

Chapter 7 Tobacco smoking is an important modifiable risk factor for recurrent hospitalisation with pneumonia

7.1 Introduction

Preventing hospitalisation for pneumonia, especially during winter, is one of the priorities for respiratory disease in the NHS Long Term Plan, and for the British Thoracic Society. However, there are few studies related to recurrent hospitalisation for pneumonia and specifically no studies from the UK. Studies from the past two decades suggest recurrent hospitalisation for pneumonia occurs in 9-17.6% of adults during a follow-up of 1-3 years following index admission with pneumonia.[264,269,270] Non-modifiable factors associated with increased risk of recurrent pneumonia include increasing age, impaired functional status, comorbidities and medications.[271] Unexpectedly, two previous studies found that smoking status at index admission was not independently associated with the risk of recurrent pneumonia.[57,265] This finding contrasts with the well-described dose-dependent association of tobacco smoking with the development of pneumonia.[205]

The aims of this study were to determine the incidence of recurrent hospitalisation with pneumonia in England, the association of tobacco smoking as a potentially modifiable risk factor, and to describe the proportion of current smokers admitted with pneumonia who were offered stop smoking interventions.

7.2 Methods

7.2.1 Study population and follow-up

Adults aged ≥18 years with the first episode of hospitalisation for pneumonia (index date) recorded in HES between 1 July 2002 and 30 June 2017 were included. The 'epidemiological year' definition of July- June was used as the unit of time in order to avoid the winter peak of pneumonia traversing two calendar years. Pneumonia was

defined based on J12- J18 ICD-10 codes recorded as the primary code for the first episode of hospitalisation. Patients were excluded if they had less than a year of time registered to the practice before admission, were admitted for at least a day in the 10 days preceding the index admission (identified from HES) or readmitted to hospital within 30 days of discharge.

Previous studies have defined recurrent pneumonia as a discrete episode of pneumonia separated by a variable interval of 30-90 days after the index pneumonia, a radiographic clearing of the acute infiltrate or both.[57,265,270,272–274] Patients are believed to have achieved 'clinical cure' or recovered from pneumonia when there is resolution of signs and symptoms related to pneumonia without recurrence.[50] Radiographic clearance of CAP varies between 50.6% at 2 weeks to 66.7% at 4 weeks, with slower clearance in older patients.[51,52] Bruns et al. reported physician-based clinical cure in 88.9% at 28 days after hospitalisation for mild to moderate CAP, though radiological resolution was seen in 68.4% and symptoms were completely resolved in only 41.7%, highlighting the discordance between physician rated clinical cure, radiographic resolution and patient reported symptoms.[53] In this study, readmission within 30 days of discharge was considered to be readmission for the index episode, accepting the limitation that some patients may have been readmitted for the index pneumonia.

Patients were followed up from day one after the date of discharge from hospital to either the date of admission for recurrent pneumonia, end of data collection (30 June 2017), date of transfer out of practice, date of last data collection for the practice or date of death, whichever came first.

7.2.2 Definitions

Read code lists for smoking status and stop smoking interventions were developed using a combination of validated medical Read codes and product Read codes under British National Formulary (BNF) listing of "Drugs used in substance dependence: Nicotine dependence" (Appendix 10).[70,76] The most recent documented smoking status (current, ex and never smokers) in CPRD before the index admission was used.

7.2.3 Statistical analysis

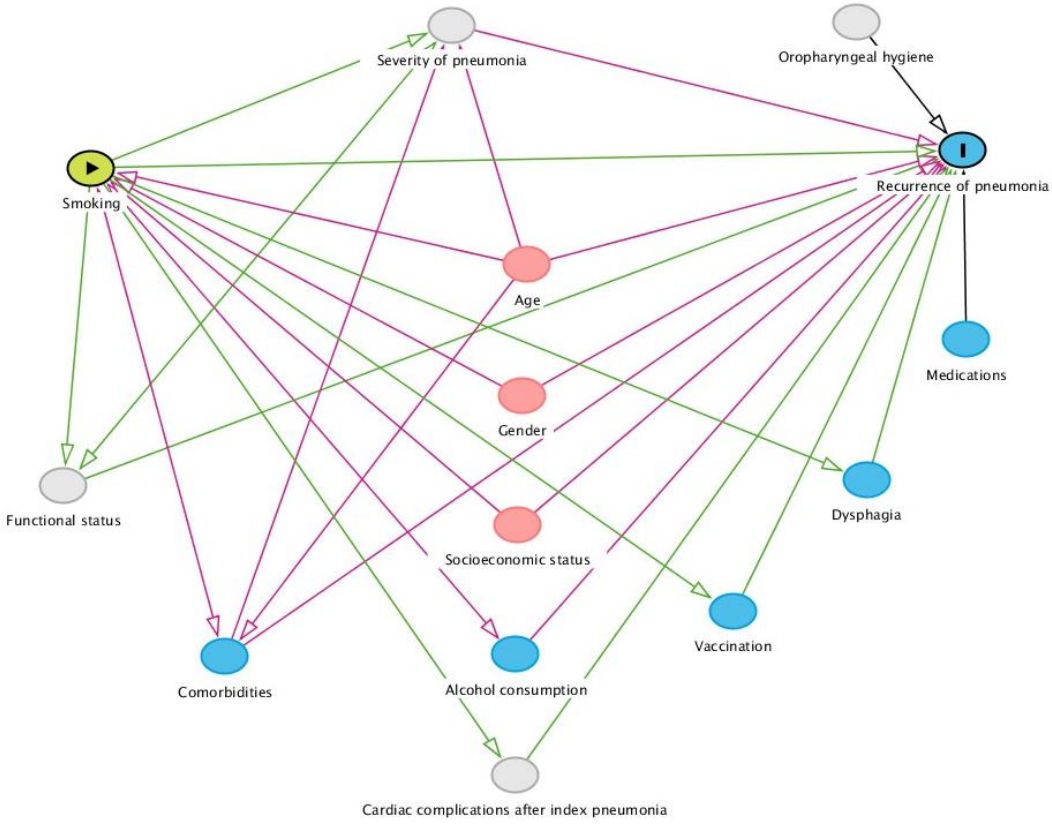
Descriptive statistics for the patient population were calculated. 'Time to first recurrence' was measured from day one after discharge from hospital to admission with recurrent pneumonia. Incidence rates (per 100 person-years) for recurrent pneumonia at different time intervals were determined; 90 days, 1 year and 5 years. The proportion of patients who developed recurrent pneumonia at 90 days and 1 year were determined. Cumulative incidence rates for recurrent pneumonia were plotted using the Nelson-Aalen plot. Proportion of current smokers who received stop smoking interventions a year before index pneumonia admission and at 90 days, 6 months and 12 months after discharge were determined.

Directed acyclic graph (DAG) was used to identify the minimum set of confounders to close the back-door paths, which included age, gender, deprivation, alcohol consumption and comorbidities (

Fig 7-1). Multiple imputation using chained equations was performed with 10 imputed datasets for smoking status (2.9% missing data) and alcohol consumption (15.1% missing data). Competing-risks regression analyses were conducted to determine the effect of tobacco smoking on hospitalisation for recurrent pneumonia with death as a competing

event. The proportion of patients who quit smoking after hospitalisation for index pneumonia was determined. Statistical analyses were performed using StataMP/ 15.1.

Fig 7-1: Directed Acyclic Graph illustrating the association between smoking status (exposure) and developing recurrence of pneumonia (outcome).

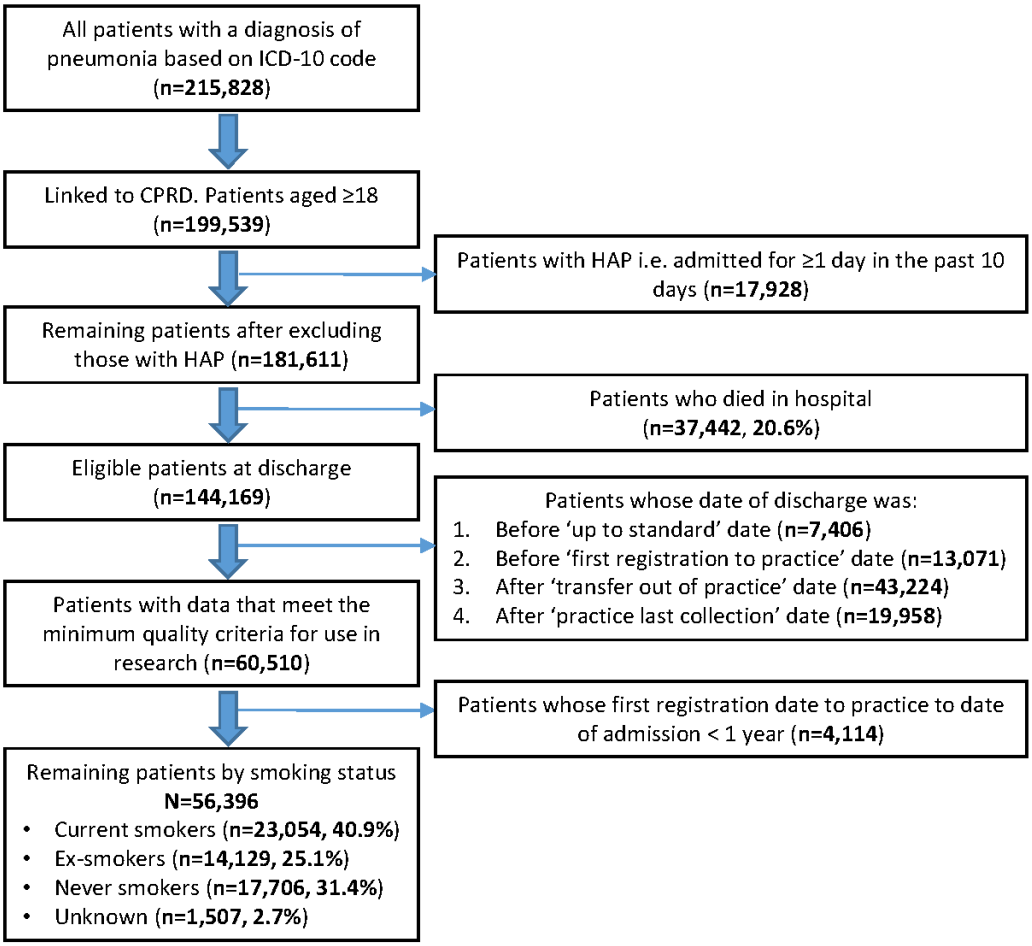


*Functional status, severity of pneumonia, cardiac complications after index pneumonia and oropharyngeal hygiene were not measured in this study.

7.3 Results

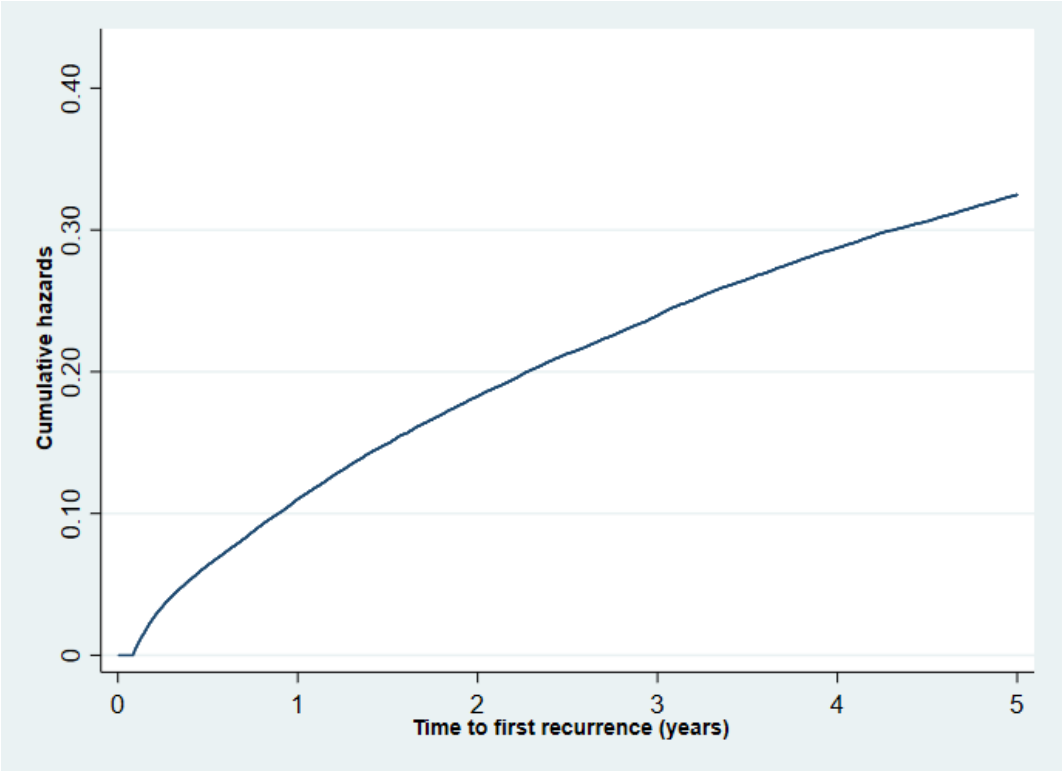
The study cohort comprised 56,396 patients (**Fig 7-2**).

Fig 7-2: Flowchart of study population



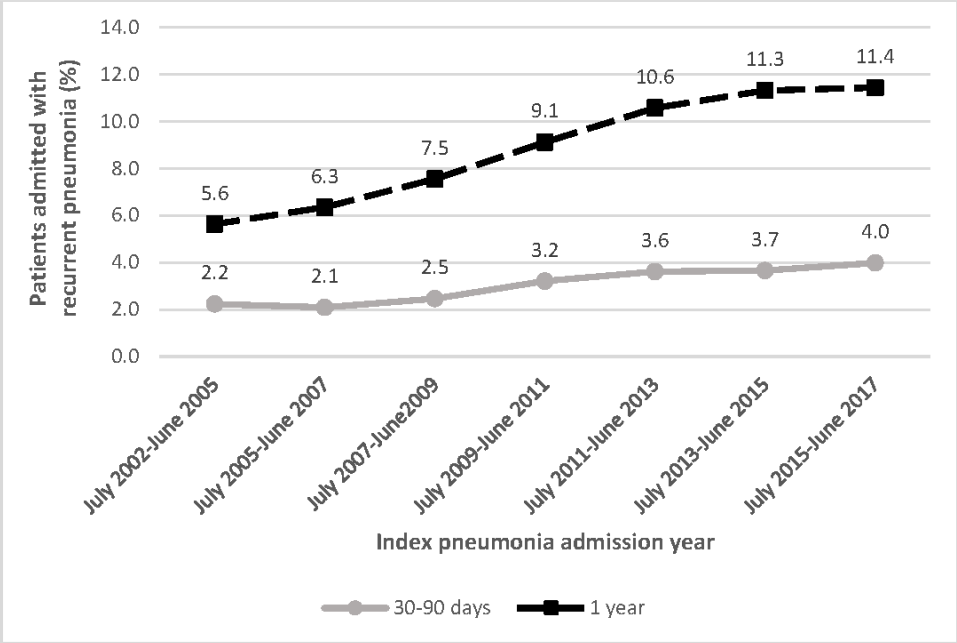
The median time to recurrence was 1.3 years (IQR 0.5-2.6 years). The incidence rates (per 100 person-years) for recurrent pneumonia at 90 days, 1 year and 5 years were 13.6 (95% CI 13.0-14.2), 11.1 (95% CI 10.8-11.4) and 7.10 (95% CI 6.97-7.23) correspondingly. The cumulative incidence is illustrated in **Fig 7-3**.

Fig 7-3: Nelson-Aalen plot of cumulative incidence of pneumonia recurrence in the first 5 years after index pneumonia



Within 90 days and 1 year of follow-up, 1,733 (3.1%) and 5,064 (9.0%) developed recurrent pneumonia respectively, with 1,866 (36.9%) patients hospitalised for more than one recurrence during the 1-year follow-up period. The 30-day mortality for a recurrent pneumonia hospitalisation was 23.7% (n=3,011). Over the period 2002 to 2017, the proportion of recurrent pneumonia within one year of index admission increased from 5.6% to 11.4% (**Fig 7-4**).

Fig 7-4: Trend of recurrence of pneumonia within 30-90 days and 1 year of index pneumonia admission



Note: 1-year recurrence refers to recurrence between 30-365 days after discharge for index pneumonia. Patients readmitted to hospital within 30 days of discharge were considered to be readmissions for the index episode, hence excluded.

Current smoking at index admission was independently associated with a 42% increased risk of recurrent pneumonia compared to having never smoked at any point in time (**Table 7-1**). This risk was halved in ex-smokers. Of note, ex-smokers had quit smoking for a median of 25.5 years (IQR 15.2-36.9) prior to index CAP; data were available in 69.5% ex-smokers (n=9,814). Other factors independently associated with an increased risk of recurrent pneumonia were increasing age, male gender, residence in the most deprived quintile and higher Charlson Comorbidity Index score.

Table 7-1: Factors independently associated with recurrent pneumonia within a year of discharge: Competing-risks regression (CRR) analysis with death as competing event

	Without recurrence n (%)		With recurrence n (%)		Multivariate CRR sHR (95% CI)		p value
Number of patients	51332		5064				
Smoking status							
Never	16932	(93.0)	1274	(7.0)	1.00	Reference	
Ex	12995	(89.5)	1517	(10.5)	1.24	(1.15-1.34)	<0.001
Current	21405	(90.4)	2273	(9.6)	1.42	(1.32-1.53)	<0.001
Age							
18-49	7961	(97.0)	247	(3.0)	1.00	Reference	
50-64	8274	(93.7)	556	(6.3)	1.76	(1.51-2.05)	<0.001
65-74	9513	(90.6)	986	(9.4)	2.37	(2.05-2.75)	<0.001
75-84	13625	(89.0)	1692	(11.0)	2.78	(2.41-3.22)	<0.001
≥85	11959	(88.3)	1583	(11.7)	3.17	(2.73-3.67)	<0.001
Gender							
Male	25283	(90.3)	2719	(9.7)	1.00	Reference	
Female	26049	(91.7)	2345	(8.3)	0.85	(0.80-0.90)	<0.001
Alcohol status							
Non-drinker	13329	(90.2)	1451	(9.8)	1.00	Reference	
Former drinker	2938	(88.5)	381	(11.5)	1.08	(0.96-1.22)	0.176
Occasional drinker	8193	(90.6)	854	(9.4)	0.95	(0.87-1.04)	0.237
Moderate drinker	19696	(91.7)	1772	(8.3)	0.88	(0.82-0.95)	0.001
Heavy drinker	7176	(92.2)	606	(7.8)	0.90	(0.81-1.01)	0.063
IMD (patient-level)							
1 (least deprived)	9721	(91.7)	875	(8.3)	1.00	Reference	
2	10384	(91.0)	1023	(9.0)	1.06	(0.97-1.16)	0.195
3	10841	(91.0)	1068	(9.0)	1.06	(0.97-1.16)	0.228
4	10286	(91.3)	977	(8.7)	1.02	(0.93-1.12)	0.689
5 (most deprived)	10054	(90.0)	1117	(10.0)	1.21	(1.10-1.32)	<0.001
Unknown	46	(92.0)	4	(8.0)	1.14	(0.45-2.89)	0.776
Charlson Index							
0	13028	(95.5)	608	(4.5)	1.00	Reference	
1	11335	(92.2)	955	(7.8)	1.43	(1.29-1.59)	<0.001
2	8926	(90.1)	986	(9.9)	1.65	(1.48-1.84)	<0.001
3	6910	(88.9)	867	(11.1)	1.76	(1.58-1.97)	<0.001
4	4462	(87.6)	634	(12.4)	1.90	(1.69-2.14)	<0.001
≥5	6671	(86.8)	1014	(13.2)	2.00	(1.79-2.23)	<0.001
Co-morbidities							
COPD	9988	(84.7)	1810	(15.3)	1.77	(1.65-1.89)	<0.001
Asthma	11876	(89.0)	1471	(11.0)	1.11	(1.03-1.18)	0.004
***Chronic lung disease**	790	(88.2)	106	(11.8)	1.56	(1.29-1.90)	<0.001
Congestive cardiac failure	4943	(87.5)	705	(12.5)	1.12	(1.02-1.23)	0.016
Myocardial infarction	4654	(88.3)	614	(11.7)	1.03	(0.94-1.13)	0.496

***Other cardiac diseases**	20982	(90.0)	2344	(10.1)	1.05	(0.98-1.12)	0.149
Malignancy	10995	(88.7)	1402	(11.3)	1.17	(1.10-1.25)	<0.001
Chronic renal disease	9631	(87.8)	1343	(12.2)	1.16	(1.09-1.24)	<0.001
Cerebrovascular disease	5609	(88.0)	768	(12.0)	1.05	(0.97-1.12)	0.228
Diabetes mellitus	8394	(89.4)	996	(10.6)	1.14	(1.05-1.23)	0.001
Cognitive impairment	5174	(88.7)	660	(11.3)	1.11	(1.02-1.21)	0.017
Liver disease	478	(90.0)	53	(10.0)	1.24	(0.94-1.62)	0.128

*Chronic lung disease excluding COPD and asthma

[#] Other cardiac diseases excluding CCF and MI (e.g. hypertension, arrhythmias, valvular heart disease, conduction disorder of the heart, pericarditis, myocarditis)

Two multivariate models were conducted: Model 1: all variables + Charlson Comorbidity Index (without individual comorbidities) and Model 2: all variables + individual comorbidities (without Charlson Comorbidity Index). Results are presented from Model 1, except for individual comorbidities from Model 2 as estimates for other variables in both models were similar

Approximately 40% of current smokers received stop smoking interventions a year before admission for index pneumonia (**Table 7-2**). Of these, 2.6% (n=253) received stop smoking interventions on the day of admission to hospital and a further 11.7% (n=1,126) received advice two weeks prior to admission. After discharge, 30% of current smokers received stop smoking interventions within a year.

Table 7-2: Current smokers who were given stop smoking interventions before admission for index pneumonia or after discharge

Stop smoking interventions	**Before admission**	**After discharge***		
	1 year	**90 days**	**6 months**	**1 year**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Given	9599 (41.6)	3353 (14.5)	4831 (21.0)	6805 (29.5)

*From date of discharge to 90 days, 6 months and 1 year respectively

A change of smoking status from current smoker to ex-smoker was documented in primary care in 31.7% (n=7,312) within 12 months of discharge. This dropped to 21% (n=4,848) in the subsequent year.

7.4 Discussion

7.4.1 Principal findings

This study investigated the incidence of, and risk factors for recurrent hospitalisation for pneumonia. Within 90 days and 1 year of follow-up, 1,733 (3.1%) and 5,064 (9.0%) developed recurrent pneumonia respectively. Current tobacco smoking status at index hospitalisation for pneumonia was independently associated with a higher risk of recurrent pneumonia. Approximately 40% of patients hospitalised with pneumonia received stop smoking interventions in the year before and 30% in the year after admission for index pneumonia.

7.4.2 Comparison with other studies

Recurrent pneumonia

Studies from other countries having reported a range of incidences of recurrent pneumonia over different time-periods; 16.3% during a median follow-up of 475 days in Japan to 3.5% over an 11-year period in Sweden.[264,273] Marked differences in study methodology and healthcare system are likely to account for the variation, emphasising the importance of country-specific data. Our results are similar to data from Canada and Sweden; 2% recurrent pneumonia at 30 to 90 days from index admission, and 17.6% recurrent pneumonia during a mean follow-up of under 3 years.[57,270] Of note, we observed a 23.7% 30-day mortality for recurrent pneumonia, twice as high as 30-day inpatient mortality for index pneumonia based on BTS National Audit data.[30] Similarly, Ishifuji *et al.* found that patients with recurrent pneumonia were almost three times more likely to have fatal outcomes during over a year's follow-up compared to those without (HR 2.81, $p<0.001$).[264] Our study also revealed a significant trend of increasing proportion of recurrent pneumonia between 2002- 2017. Conversely, the BTS National

Pneumonia Audit observed a decrease in mortality from index pneumonia over a ten-year period (2009 to 2019).[30] Whether these trends in survival are related to the trends in pneumonia recurrence requires further investigation.

Tobacco smoking is associated with an increased risk of developing CAP.[205] We extend this observation to an association between tobacco smoking status at the time of index hospitalisation and recurrent pneumonia. In a case-control study, El Sohl *et al.* reported that current smokers were twice more likely to be admitted with recurrent pneumonia compared to never smokers (HR=2.04, 95% CI 1.48-2.82).[274] Conversely, two prospective cohort studies (Canada, n=2709 and Spain, n=1556) did not find any association between smoking and recurrent pneumonia.[57,265] These studies included younger patients (mean cohort ages 63 and 67 years).

Smoking cessation

Previous published literature have demonstrated that smoking cessation reduces the risk of developing CAP, with those having quit ≥10 years having similar risk to never smokers.[225,275,276] Yet, we found only 30% received stop smoking interventions within a year of discharge after hospitalisation for pneumonia. This is similar to the stop smoking interventions given to patients after hospitalisation for acute coronary syndrome (ACS) using a similar study design; 23% within 3 months.[277] Findings from the Smoking Toolkit Study, using monthly household surveys in England show that 7.6% quit smoking in the past 12 months, an improvement noted in June 2020 after a declining trend 2 years prior to that.

Current smokers who quit smoking after hospitalisation for any reason may relapse despite receiving stop smoking interventions. Thorley et al. reported a drop from tobacco

abstinence in 21% (4 weeks) to 14% (3 months) in the intervention group vs 19% to 14% in the usual care group whilst Murray et al. reported a drop from 38% (4 weeks) to 19% (6 months) in the intervention group vs 17% to 9% in the usual care group.[278,279] Rigotti et al. reported tobacco abstinence in 15% (usual care group)- 26% (intervention group) at 6 months.[280] Our study showed that 31.7% of current smokers quit smoking within 12 months after being hospitalised for pneumonia, and this declined to 21% in the subsequent year. Taking into account that smoking status in the trials were self-reported and validated by measuring exhaled carbon monoxide compared to coded data in our study, the higher proportion observed in our study may be due a higher level of motivation in patients hospitalised with a specific smoking-related illness (pneumonia) as opposed to patients hospitalised for any reason.[281] Smoking cessation were reported to be up to 30% in patients hospitalised with COPD and as high as 57% within a year in patients hospitalised for ACS, other smoking-related illnesses.[282–285] Studies have shown that patients admitted with a smoking-related disease during admission, alongside high confidence in quitting and having a plan to quit were more likely to be successful at quitting at 6-12 months of follow-up.[286–288]

7.4.3 Strengths and weaknesses of the study

A key strength of this study is the large sample size of over 56,000 patients which is representative of the English population, long-term follow-up and good data quality. The usage of two large validated medical record databases, HES-CPRD linkage enabled patients hospitalised with pneumonia to be accurately identified and allowed confident exclusion of patients with hospital- acquired pneumonia. We applied robust statistical methods including causal models using directed acyclic graphs (DAG) to identify potential confounders and multiple imputation to handle missing data which increase the transparency of our methodology, as well as rigor and validity of our study results.

However, there are a few limitations that warrant discussion. Firstly, although CPRD contains data from all of the UK, these data are predominantly from England and linked datasets including HES are available only from English practices. Therefore, the results from this study may not be generalisable to the rest of the UK. Secondly, in spite of the considerable efforts taken to ensure data quality, we cannot fully exclude the possibility of information bias from miscategorisation of the study exposure, confounders and outcomes. Thirdly, data regarding the type of tobacco smoked were only available in about half of the patients, with most consuming cigarettes and few consuming cigars (<5%). Fourthly, both CPRD clinical and prescription data only indicate whether smoking cessation advice was given and smoking cessation drugs were prescribed, not whether the advice directly resulted in a current smoker quitting or medications taken as recommended. Some of the 31.7% of patients who quit smoking within a year of hospitalisation for pneumonia may have done so by willpower alone and may not have received any smoking cessation advice or therapy.

7.4.4 Implications

Smoking is ranked as the commonest risk factor contributing to years of life lost in England.[289] In 2019, the proportion of current smokers in England was 13.9%, accounting for 5.7 million people.[290] The prevalence of smoking in our cohort was 40.9%. Despite the significant reduction in the prevalence of smoking in the past decade, there were more than 500,000 hospital admissions attributable to smoking in 2018-2019.[290,291] Though only 30% received stop smoking interventions within a year of discharge in our cohort, these were delivered in primary care and whilst many may have received these interventions during hospitalisation, these data were not available. Evidence-based stop smoking interventions include behavioural support, pharmacotherapy (bupropion, nicotine replacement therapy and varenicline) and very brief advice.[292] A Cochrane

review which included 50 trials reported that high intensity behavioural interventions initiated during hospitalisation and continue for at least a month after discharge promote smoking cessation irrespective of admitting diagnosis.[293] This highlights the importance of referring patients to a Stop Smoking Service during hospitalisation for pneumonia and the subsequent continuous support that patients need upon discharge. All healthcare professionals, both in primary and secondary care should routinely provide brief advice to all current smokers.[294] If patients are not ready to quit in hospital, close communications with primary care physicians are paramount so that they could opportunistically intervene against smoking at a future routine consultation in the community.[295]

Smoking is estimated to cost the economy in excess of £11 billion annually.[296] Of these, £2.5 billion fell to the NHS with primary care consultations and smoking-related hospital admissions, including pneumonia. Stop smoking interventions are highly cost-effective.[292] The British Thoracic Society smoking cessation audit in 2019 revealed that only 1 in 8 patients admitted to acute hospitals were referred to smoking cessation service.[297] The UK and devolved governments recognise that reducing the prevalence of smoking and harm caused by tobacco use are important public health issues, thus have developed a number of strategies for wider tobacco control.[296,298–300]

7.4.5 Conclusion

In conclusion, our findings confirm a high and rising incidence of recurrent hospitalisation for pneumonia in England, and that current smoking status at index admission is associated with an increased risk of recurrent pneumonia. Our study also provides an insight into stop smoking interventions given to patients in primary care before and after being hospitalised for pneumonia. Our findings support smoking cessation interventions

as a key component of pneumonia management, in accordance with the NHS Long Term Plan.

Chapter 8

Chapter 8 Co-infection in COVID-19: A retrospective multicentre study in patients admitted to the Intensive Care Unit

8.1 Introduction

During previous viral pandemics, reported co-infection rates and implicated pathogens have varied. In the 1918 influenza pandemic, an estimated 95% of severe illness and death was complicated by bacterial co-infection, predominantly *Streptococcus pneumoniae* and *Staphylococcus aureus.*[301]

As of 3 September 2020, over 25 million cases and 850 000 deaths due to COVID-19 infection have been reported world-wide.[302] The symptoms associated with COVID-19 infection are relatively non-specific. Fever and lower respiratory tract symptoms, such as a cough or breathlessness, are common in patients who require hospital care and radiological changes consistent with pneumonia are evident in up to 97% of these patients.[303] Confirmation of acute COVID-19 infection is reliant on a positive SARS-CoV-2 polymerase chain reaction (PCR) test result. The immune response to SARS-CoV2 infection includes a rise in IL-6 and C-reactive protein (CRP), with higher levels associated with more severe disease.[198,304]

The contribution of secondary or co-pathogens to COVID-19 infection is not well understood. The lack of an effective anti-viral agent against SARS-CoV2 combined with challenges in differentiating secondary bacterial co-infection from severe COVID-19 infection alone, has fostered the widespread use of empirical antibiotics in the immediate management of patients hospitalised with COVID-19 infection. Over the spring wave of the pandemic, 83.1% of hospitalised patients received empirical antibiotic treatment.[305]

The utility of specific biomarkers such as procalcitonin to guide antibiotic therapy in severe respiratory tract infection, and specifically COVID-19 infection, is as yet uncertain.[306,307] In the meantime, a better understanding of the incidence of co-infection in patients with COVID-19 infection and the pathogens involved is necessary for effective antimicrobial stewardship. The primary objective of this study was to determine the rate of laboratory-proven co-infection in critically ill adults with COVID-19 infection in England. Secondary aims were to describe the organisms, the characteristics of patients with co-infection and the antibiotic susceptibilities of identified bacteria.

8.2 Methods

8.2.1 Data source

A retrospective observational multicentre study of co-infection in adults with confirmed COVID-19 requiring intensive care unit (ICU) admission was performed. Seven acute hospitals from across England participated in the study including large (>1000 beds) tertiary hospitals and medium (500- 1000 beds) district hospitals: Nottingham University Hospitals NHS Trust, Newcastle Upon Tyne Hospitals NHS Foundation Trust, Brighton and Sussex University Hospitals NHS Trust, Guy's and St Thomas' NHS Foundation Trust, Salford Royal NHS Foundation Trust, University Hospitals of Derby and Burton NHS Foundation Trust and University College London Hospitals NHS Foundation Trust.

8.2.2 Study population

Case inclusion criteria were adults aged >16 years with completed ICU admissions (discharged from or died whilst in ICU) for COVID-19 pneumonia (i.e. requiring Level 2 or Level 3 care according to the classification by the Intensive Care Society, UK) from disease emergence to 18 May 2020. SARS-CoV-2 was confirmed using reverse transcriptase-

polymerase chain reaction (RT-PCR) from a respiratory specimen. Participating sites were asked to enter data for either: 1) all identified patients, or 2) a random selection of at least ten patients from across their eligible cohort. Where more than one critical care area existed at a participating site, a random selection from across areas was requested to avoid selection bias. Exclusion criteria were defined as: COVID-19 infection diagnosed >48 hours after hospital admission or a hospital admission in the last 14 days (hospital-acquired COVID-19) and patients transferred into ICU from a different hospital.

8.2.3 Data collection

Personal information was removed at the point of participating site data entry onto a secure online database platform (REDCap Cloud). Data were gathered from electronic medical records. Fields collected were: demographics (age, gender, ethnicity, presence or absence of co-morbidity as defined in the Intensive Care National Audit & Research Centre (ICNARC) report on COVID-19 in critical care and type 2 diabetes mellitus); hospital admission details (date, days of symptom onset prior to admission and radiology findings); ICU details (date of admission, mechanical ventilation during the first 24 hours, advanced respiratory support (**Table 8-1**), acute physiology and chronic health evaluation (APACHE II) score and outcomes); antibiotics received and all microbiology test results to the end of the ICU admission (including any identified antimicrobial resistance).

Table 8-1: Definition (based on ICNARC report on COVID-19 in critical care)[308]

Comorbidities must have been evident within the six months prior to critical care and documented at or prior to critical care: • Cardiovascular: symptoms at rest • Respiratory: shortness of breath with light activity or home ventilation • Renal: renal replacement therapy for end-stage renal disease • Liver: biopsy-proven cirrhosis, portal hypertension or hepatic encephalopathy • Metastatic disease: distant metastases • Haematological malignancy: acute or chronic leukaemia, multiple myeloma or

lymphoma • Immunocompromise: chemotherapy, radiotherapy or daily high dose steroid treatment in previous six months, HIV/AIDS or congenital immune deficiency • Type II diabetes mellitus
Mechanical ventilation during the first 24 hours was identified by the recording of a ventilated respiratory rate, indicating that all or some of the breaths or a portion of the breaths (pressure support) were delivered by a mechanical device. This usually indicates invasive ventilation; BPAP (bi-level positive airway pressure) would meet this definition but CPAP (continuous positive airway pressure) does not.
Advanced respiratory support was defined as invasive ventilation, BPAP via trans-laryngeal tube or tracheostomy, CPAP via trans-laryngeal tube, extracorporeal respiratory support.

8.2.4 Definitions

Diagnostic microbiology tests were performed as per standard testing protocols within NHS laboratories at individual participating sites. Microbiology results included in the analysis were: standard culture (blood, sputum, tracheal-aspirate, bronchoalveolar lavage (BAL), urine) and validated culture-independent tests such as respiratory viral PCR (**Table 8-2**) and urinary antigens. Co-infection was defined as present if a likely pathogen was identified in a clinical sample taken for diagnostic purposes. Culture results were considered to represent contamination in the following situations: blood cultures yielding common skin contaminants in a single sample (Coagulase-negative Staphylococci, *Micrococcus spp*., viridans group streptococci, *Propionibacterium spp*., *Corynebacterium spp*., *Bacillus spp.*) without a concurrent positive culture from an indwelling line tip[309–311], *Candida spp*. cultured from respiratory and urinary catheter samples[312,313], respiratory samples yielding Gram-positive organisms typically present in the oropharyngeal flora[314], growth of *Enterococcus spp.* in a single catheter urinary specimen.[315] Despite this effort, culture results from some non-sterile respiratory samples may represent colonisation, hence the term co-infection/ co-colonisation is used for respiratory samples. Radiology findings were defined based on the COVID-19 British Society of Thoracic Imaging

reporting template.[316] Where both chest CT and CXR findings were available, chest CT findings were prioritised.

Table 8-2: Viral testing panel by study site

Study site	Viral testing panel
Nottingham University Hospitals	Influenza A & B, RSV, Rhinovirus, Enterovirus, Adenovirus, Parechovirus, Parainfluenza pool (types 1-4), Human metapneumovirus, Bocavirus
Newcastle Upon Tyne Hospitals	Influenza A & B, Respiratory syncytial virus (RSV), Rhinovirus, Human metapneumovirus, Adenovirus, Parainfluenza pool (types 1-4)
Brighton and Sussex University Hospitals	Influenza A & B, RSV
Guy's & St Thomas'	Influenza A & B, RSV, Enterovirus, Rhinovirus, Parainfluenza, Adenovirus, Human metapneumovirus
Salford Royal	Influenza A & B, RSV
University Hospitals of Derby & Burton	Influenza A & B, RSV, Parainfluenza, Rhinovirus, Human metapneumovirus, Adenovirus
University College London	Influenza A & B, RSV, Parainfluenza pool (types 1-4), Human metapneumovirus, Adenovirus, Rhinovirus

8.2.5 Statistical analysis

Demographics, clinical and disease characteristics were described using appropriate descriptive statistics for: i) those with co-infection, and ii) those without co-infection. Characteristics of patients in the study were also compared with the patients in the Intensive Care National Audit & Research Centre (ICNARC) report on COVID-19 in critical care, 22 May 2020. The proportion of co-infection (%) was determined at three time points: on admission, within 48 hours, and during ICU admission (from day of ICU admission to ICU discharge or death in ICU). The co-infection rate was calculated per 1000 person-days based on the first co-infection detected in hospital per patient (person-time was determined from date of hospital admission to date of first co-infection, date of discharge from ICU or date of death in ICU, whichever came first for each patient).

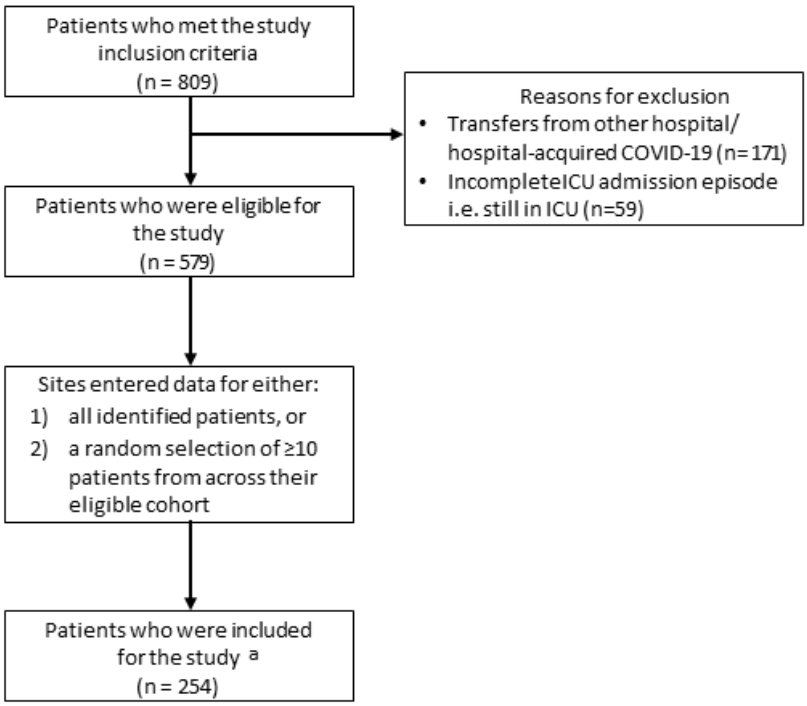
Univariate logistic regression analyses were conducted to determine the association between selected variables (age, gender, study site, ethnicity and co-morbidities) and the odds of a) developing co-infection during admission, and b) co-infection and mortality in ICU. Competing-risks regression analysis was conducted to assess if patients with co-infection had a longer length of hospital stay (from hospital admission to the end of ICU admission) than those without co-infection, with death as a competing-event. Co-pathogens were described separately for bacterial, viral and fungal infections. The proportion of bacterial co-pathogens with antimicrobial resistance was recorded.

An analysis of type of pathogens identified at different time points from admission was performed (≤48 hours and >48 hours following admission) to identify those with community vs hospital-acquired co-infection. Pathogens identified within 48 hours of hospital admission were listed by type of test performed. A sub-analysis of the hospital-acquired co-infection was performed to identify the type of pathogens detected early (3-7 days into hospital admission) and late (>7 days into hospital admission). Statistical analyses were performed using Stata MP/15.1.

8.3 Results

Of 579 eligible patients during the study period, 254 patients with completed ICU episodes were studied (**Fig 8-1, Table 8-3**).

Fig 8-1: Flowchart of study population



[a] See **Table 8-3** for exact breakdown

Table 8-3: Study population by study site

Study site	Met inclusion criteria[a]	Still in ICU[b]	Transfers from other hospital/ Hospital-acquired COVID-19[c]	Eligible[d]	Entered into database (% of those eligible)
Nottingham University Hospitals	97	11	1	85	79 (92.9)
Newcastle Upon Tyne Hospitals	100	4	20	76	48 (63.2)
Brighton and Sussex University Hospitals	58	8	4	46	45 (64.3)
Guy's & St Thomas' NHS Foundation Trust	316	0	103	213	34 (16.0)
Salford Royal	46	3	11	32	22 (68.8)
University Hospitals of Derby & Burton	54	1	0	53	16 (30.2)
University College Hospitals London	138	32	32	74	10 (13.5)
Total	809	59	171	579	254 (43.9)

d= a- (b+c)

The median age of the study cohort was 59 years (IQR 49-69, range 19-84) and 164 (64.6%) patients were male; similar to corresponding data from the ICNARC cohort (**Table 8-4**).[308] Patients were admitted to hospital between 21 Feb 2020 and 1 May 2020. The median time from onset of symptoms to admission was seven days (IQR 5-10). The median time from hospital admission to ICU admission was one day (IQR 0-2). Antibiotics were prescribed to 35 (13.8%) patients before hospital admission and to 228 (89.8%) patients within 48 hours of admission. Throughout the course of admission, 241 (94.9%) of patients received antibiotics at some point.

Table 8-4: Characteristics of study population in comparison with ICNARC data

	Without coinfection n (%)	With coinfection n (%)	ICNARC data[a] n (%)
Number of patients	171 (67.3)	83 (32.7)	9026
Age			*
18-49	47 (27.5)	17 (20.5)	
50-64	51 (29.8)	42 (50.6)	
65-74	47 (27.5)	19 (22.9)	
75-84	26 (15.2)	5 (6.0)	
Gender			[N=9022]
Male	106 (62.0)	58 (69.9)	6403 (71.0)
Female	65 (38.0)	25 (30.1)	2619 (29.0)
Ethnicity			[N=8185]
White	108 (63.2)	44 (53.0)	5468 (66.8)
Black	13 (7.6)	10 (12.1)	1245 (15.2)
Asian	16 (9.4)	5 (6.0)	797 (9.7)
Mixed	3 (1.8)	2 (2.4)	138 (1.7)
Other	4 (2.3)	3 (3.6)	537 (6.6)
[§]BAME	36 (21.1)	20 (24.1)	-
Unknown	27 (15.8)	19 (22.9)	-
Co-morbidities			[N=8777]
Cardiovascular	3 (1.8)	0 (0.0)	42 (0.5)
Respiratory	0 (0.0)	2 (2.4)	74 (0.8)
Renal	3 (1.8)	2 (2.4)	144 (1.6)
Liver	0 (0.0)	0 (0.0)	33 (0.4)
Metastatic disease	0 (0.0)	0 (0.0)	38 (0.4)
Haematological malignancy	6 (3.5)	1 (1.2)	144 (1.6)
Immunocompromised	11 (6.5)	2 (2.4)	295 (3.4)
Type 2 diabetes mellitus	47 (27.5)	19 (22.9)	N/A
Indicator of acute severity			
Mechanically ventilated within first 24h			5298 (62.8)[b]
APACHE II Score, mean (SD)	13.3 (5.6)	14.2 (5.5)	14.7 (5.3)[c]
PaO2/FiO2 ratio (kPa), median (IQR); [mmHg]	17.2 (12.6-22.3); [129 (95-168)]	17.4 (11.8-23.7); [131 (88.5-178.1)]	15.8 (11.3-22.0)[d]
≤ 13.3 kPa (< 100 mmHg)	49 (28.7)	24 (28.9)	2982 (36.8)
> 13.3 and ≤ 26.7kPa (100 - 200 mmHg)	92 (53.8)	41 (49.4)	3961 (48.9)
> 26.7 kPa (> 200 mmHg)	30 (17.5)	18 (21.7)	1161 (14.3)
LOS from hospital admission to the end of ICU admission (days), median (IQR)			
Survivors	9 (4-14)	22 (17-27)	N/A
Non-survivors	7 (4-12)	17 (11-20)	

[a] Intensive Care National Audit & Research Centre (ICNARC) report from 22 May 2020[308]
* Median age= 60 (51-68)
[§] BAME is the total of Black, Asian, Mixed and Other ethnicities
Denominators: [b] N=8433, [c] N=8648 and [d] N=8104

The overall median length of stay (LOS) in ICU was nine days (IQR 4-17); 10 days (IQR 4-18) for survivors and nine days (IQR 5-15) for non-survivors. One hundred and fifty-one patients (59.5%) were mechanically ventilated within 24 hours of admission, and 158 patients (62.2%) received advanced respiratory support (invasive ventilation, CPAP via trans-laryngeal tube, extracorporeal respiratory support) during admission. Of those who were discharged from ICU (n=172 patients), two patients (1.2%) died in hospital, 147 patients (85.5%) were discharged from hospital and 23 patients (13.4%) remained in hospital at the end of the study.

All patients had either a CXR (n=246 patients) and/or a chest CT scan (n= 74 patients). Classic/ probable COVID-19 radiographic changes were recorded in 209 patients (82.3%), five (2%) had normal imaging, 27 (10.6%) had indeterminate changes and 13 (5.1%) had non-COVID19 findings.

In total, co-infection/ co-colonisation was identified in 83 (32.7%) patients from hospital admission to the end of ICU stay; median time to co-infection/ co-colonisation was 9 days (IQR 6-14). The list of identified potential pathogens and contaminants from standard cultures (blood, BAL, sputum and tracheal aspirate) is available in Appendix 11. On the day of admission, potential co-pathogens were identified in four patients (1.6%), rising to 14 (5.5%) patients within the first 48 hours of hospital admission. Fifteen potential pathogens were identified from 14 patients within 48 hours; 14 bacterial and one viral pathogen (**Table 8-5**). None of these potential pathogens were identified from blood culture.

Table 8-5: Organisms identified within 48 hours of hospital admission

Type of test	Potential Pathogens	No of pathogens
Tracheal aspirate or sputum culture		
	Escherichia coli	1
	[a]*Pseudomonas sp*	1
	Pseudomonas aeruginosa	1
	Enterobacter cloacae complex (AmpC)	1
	[a]*Staphylococcus aureus* (MSSA)	2
BAL PCR/ culture		
	[b]*Staphylococcus aureus* (MSSA & MRSA)	2
	Klebsiella pneumoniae	1
Other tests		
Pneumococcal urinary antigen test	[a]*Streptococcus pneumoniae*	2
MSU	*Escherichia coli*	2
RT-PCR	*Mycoplasma pneumoniae*	1
	[a]*Metapneumovirus*	1

[a] Pathogens identified on the day of admission (*Pseudomonas sp*, one out of two *MSSA* and one out of two *S.pneumoniae identified,* and *Metapneumovirus*), total= 4

[b] *One out of two organisms was Methicillin-resistant Staphylococcus aureus (MRSA).* The same patient also had MRSA in pleural fluid culture after 48 hours into hospital admission.

In a sensitivity analysis excluding the hospital which contributed a third of cases, the 48-hour co-infection/ co-colonisation rate remained similar (**Table 8-6**).

Table 8-6: Co-infection rate within 48 hours (1000 person-days) for the overall study population and excluding the hospital which contributed a third of cases.

	Co-infection rate within 48 hours (1000 person-days) (95% CI)
Overall	28.2 (16.7-47.7)
Excluding Nottingham University Hospitals	32.0 (17.7-57.8)

The commonest potential co-pathogen within 48 hours of hospital admission was *S.aureus,* three methicillin-susceptible (MSSA) and one methicillin-resistant *S.aureus* (MRSA) (4 patients). Two positive Mycoplasma IgG/ IgM tests in separate patients were

deemed false positives and excluded from the analysis. The number of tests performed within 48 hours of hospital admission are listed in **Table 8-7**, by type of tests. For bacterial co-pathogens, the antimicrobial susceptibilities are described in **Table 8-8**.

Table 8-7: Number of tests performed within 48 hours of hospital admission, by type of tests

Type of tests	On admission		After admission (within 48 hours)		Overall	
	n	N	n	N	n	N
Blood culture	223	174	89	46	312	220
BAL PCR/ culture, sputum culture, tracheal culture	18	15	34	31	52	46
Urinary pneumococcal antigen	25	25	55	51	80	76
Urinary legionella antigen	36	34	55	54	91	88
Respiratory viral PCR	119	106	32	22	151	128

Legend:
n= Number of tests done
N= Number of patients who had the test

Table 8-8: Antimicrobial susceptibilities for identified bacterial pathogens

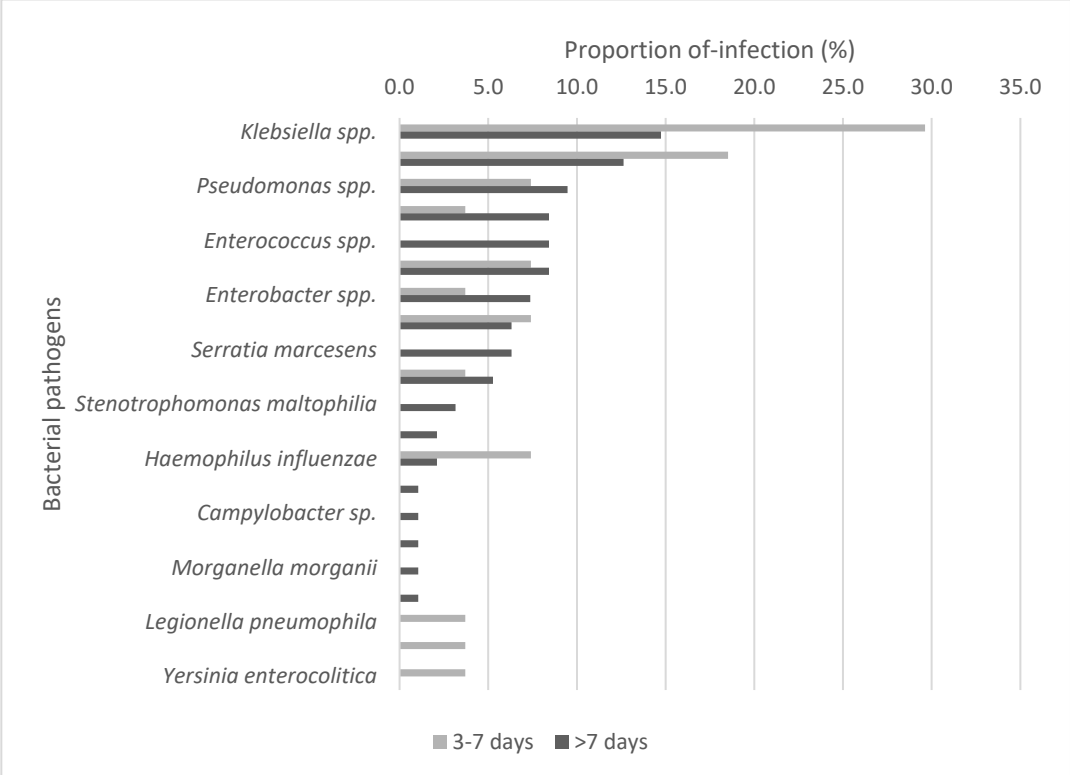
	AMR	No AMR	Unknown	Total	Resistance n (%)
Klebsiella spp.	10	4	2	16	Co-amoxiclav, 2 (20); Cefuroxime, 7 (70); Piperacillin/Taz, 5 (50); Meropenem, 1 (10); Co-trimoxazole, 1 (10); Trimethoprim, 1 (10); Chloramphenicol, 1 (10)
Escherichia coli	11	9	0	20	Amoxicillin, 8 (72.7); Co-amoxiclav, 5 (45.5); Meropenem, 1 (9.1); Ertapenem, 1 (9.1)
Enterobacter aerogenes	3	2	0	5	Cefuroxime, 2 (40); Cefadroxil, 1 (20); Ceftazidime, 1 (20); Meropenem, 1 (20); Gentamicin, 1 (20)
Pseudomonas spp.	7	4	2	13	Ciprofloxacin, 2 (28.6); Ceftazidime, 2 (28.6); Piperacillin/Taz, 5 (71.4); Meropenem, 3 (42.9); Gentamicin, 1 (14.3); Amikacin, 1(14.3); Ticarcillin/ clavulanate, 1 (14.3)
Serratia marcescens	1	0	0	1	Piperacillin/Taz, 1 (100)
Citrobacter koseri	1	3	1	5	Piperacillin/Taz, 1(100); Meropenem, 1 (100)
Staphylococcus aureus	4	7	0	11	Flucloxacillin, 1 (25); Doxycycline, 2 (50); Clarithromycin, 3 (75); Clindamycin, 1(25)
Haemophilus influenzae	3	0	1	4	Amoxicillin, 3 (100); Co-amoxiclav, 3 (100); Cefuroxime, 2 (66.7); Doxycycline, 1 (33.3)
Acinetobacter baumanii	1	1	0	2	Ceftazidime, 1 (100)
Burkholderia multivorans	1	0	0	1	Meropenem, 1 (100); Ceftolozane/Tazobactam, 1 (100)
Enterococcus spp.	1	3	4	8	Amoxicillin, 1 (100); Gentamicin, 1 (100)
Morganella morganii	1	0	0	1	Cefuroxime, 1 (100); Piperacillin/Taz, 1 (100)
Raoultella sp.	1	0	0	1	Piperacillin/Taz, 1 (100)
Total	45	33	10	88	

Legend

- AMR is defined as resistance reported to one or more antimicrobial agents tested (excluding intrinsic resistances).[317] Information in this table is based on the antimicrobial patterns released by individual sites for clinicians, other resistance may have been present but not reported
- Piperacillin/Taz= Piperacillin/Tazobactam
- Co-pathogens (with AMR) breakdown by species
    - *Klebsiella spp.: Klebsiella pneumoniae (2), Klebsiella aerogenes (7), Klebsiella voriicola (1)*
    - *Pseudomonas spp.: Pseudomonas sp (1), Pseudomonas aeruginosa (6)*
    - *Enterococcus spp.: Enterococcus faecium (1)*

Beyond 48 hours of hospital admission to the end of ICU stay, 124 potential co-pathogens were identified in 77 (30.3%) patients; 29 potential pathogens from Days 3 – 7 and 95 potential pathogens from Day 8 onwards (**Fig 8-2**). The co-infection/ co-colonisation rate >48 hours after admission was 27.0 per 1000 person-days (95% CI 21.3-34.1). All were bacterial pathogens (n=122) except for two fungal organisms. The commonest potential co-pathogens identified were Gram-negative bacteria, including *Klebsiella spp.* (23 patients) and *Escherichia coli* (20 patients). No viral co-pathogens were detected. Of the two fungal co-pathogens, one was *Aspergillus fumigatus* from a tracheal aspirate culture obtained on Day 5 in a 54-year old male. The other was *Candida parapsilosis* from a blood culture taken at Day 7 in a 55-year old lady. Neither patient had any pre-existing co-morbidities.

Fig 8-2: Bacterial pathogens detected after 48 hours of hospital admission; 124 potential pathogens detected



Reported as proportion (%) of the total number of bacterial pathogens detected within '3-7 days' and '>7 days' from hospital admission.

On univariate analyses, patients aged 50-64 years were more likely to have a co-infection/ co-colonisation than those aged 18-49 years. No other significant association was found (**Table 8-9**). Patients with co-infections/ co-colonisation were more likely to die in ICU (with coinfections/ co-colonisation, n=34 vs without coinfections/ co-colonisation, n=48, crude OR 1.78, 95% CI 1.03-3.08, p=0.04) and had a longer hospital LOS (measured from admission to hospital to the end of ICU admission, subhazard ratio (likelihood of discharge from ICU) = 0.53, 95% CI 0.39-0.71, p< 0.001).

Table 8-9: Univariate logistic regression analyses investigating the association between variables of interest and odds of developing co-infection/ co-colonisation.

	Crude OR (95% CI)	**p value**
Number of patients		
Age		
18-49	1 (Reference)	
50-64	2.28 (1.14-4.53)	0.019*
65-74	1.12 (0.52-2.41)	0.777
75-84	0.53 (0.18-1.61)	0.263
Gender		
Male	1 (Reference)	
Female	0.70 (0.40-1.23)	0.218
Ethnicity		
White	1 (Reference)	
Black	1.89 (0.77-4.62)	0.164
Asian	0.77 (0.26-2.22)	0.625
Mixed	1.64 (0.26-10.13)	0.597
Other	1.84 (0.40-8.57)	0.437
[α]BAME	1.36 (0.71-2.61)	0.349
Unknown	1.73 (0.87-3.42)	0.117
Co-morbidities		
Cardiovascular	-	
Respiratory	-	
Renal	1.38 (0.23-8.43)	0.725
Liver	-	
Metastatic disease	-	
Haematological malignancy	0.34 (0.04-2.83)	0.316
Immunocompromise	0.36 (0.08-1.65)	0.187
Type 2 diabetes mellitus	0.78 (0.42-1.44)	0.434

*p value of <0.05 denotes a significant difference
[#] median and IQR
[α]BAME is the total of Black, Asian, Mixed and Other ethnicities

8.4 Discussion

8.4.1 Principal findings

Bacterial co-infection/ co-colonisation within 48 hours of hospital admission for COVID-19 infection in adults was uncommon; 1.6% on admission and 5.5% within 48 hours. The commonest pathogens identified within the first 48 hours of hospital admission were *Staphylococcus aureus* and *Streptococcus pneumoniae.* The proportion of co-pathogens detected increased with duration of ICU stay and consisted largely of Gram-negative bacteria, particularly *Klebsiella pneumoniae* and *Escherichia coli*. The co-infection/ co-colonisation rate >48 hours after admission was 27.0 per 1000 person-days (95% CI 21.3-34.1).

8.4.2 Comparison with literature:

Concern regarding co-infection during viral pandemics, specifically respiratory co-infection with a bacterial pathogen, is borne from previous experience in influenza. During the 2009 H1N1 influenza A pandemic, early co-infection rates were high; 22.5% within 72 hours of admission in adults requiring critical care.[318] In contrast, limited evidence from studies of Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome suggest lower co-infection rates (10.3 to 18.5%).[319,320] In COVID-19, systematic reviews based on studies predominantly from China reported low estimates (<7%) of bacterial co-infection.[321–323] In the UK, a retrospective cohort study detected early bacterial infection (0-5 days from admission) in 3.2% of all hospitalised patients (13.5% of those requiring critical care), increasing to 6.1% throughout admission.[324]

Youngs *et al.* reported bacterial co-infection within 48 hours of admission to ICU in 8% of patients with COVID-19 compared to 58% of patients with influenza, with no difference in the incidence of late infection between the two groups.[325] In the US, higher early bacterial co-infection rates (16.6%) were identified by Crotty *et al.*; respiratory cultures positive for oral bacteria flora constituted 15/25 of these cases.[326] In contrast to studies that relied on predominantly culture-based techniques, Kreitmann *et al.* identified early bacterial co-infection in 27.7% (13/47) of their prospective cohort of ventilated patients using a multiplex PCR assay with only one case identified by conventional culture.[327] Variations in case definitions, diagnostic testing and geography may partly account for the differences observed between studies although overall, there is a suggestion that increased severity of disease, particularly when ICU care is required, is associated with increased rates of co-infection.

The prevalence of nosocomial infection is 20.6% and increases with duration of ICU stay.[328,329] Our observed co-infection/ co-colonisation rate is relatively high, consistent with a patient cohort with long ICU stays (median 10 days) and requiring high levels of respiratory support.

Consistent with reports from other studies, the commonest potential co-infecting bacteria identified within 48 hours of admission was *S. aureus.*[324,327,330] In patients in whom early co-infection is suspected clinically, due consideration of *S. aureus* is warranted. However, the rate of *S. aureus* co-infection is markedly lower than that observed in pandemic influenza, suggesting it is a less significant issue with COVID-19 infection.[318] The predominant late pathogens observed were Gram-negative bacteria, particularly *K. pneumoniae*. These pathogens are commonly associated with hospital and ventilator-acquired pneumonia and have been reported as common co-pathogens in

COVID-19 infections, particularly ICU cohorts.[321,322,331–333] The predominance of Gram-negative bacteria in these studies likely reflects nosocomial infection following prolonged ICU stay and empirical antibiotic use.

Viral co-pathogen was identified in one patient in our cohort; lower than the 3% (95% CI 1-6%) viral co-infection rate reported in systematic reviews and in contrast to the 20.7% viral co-detection rate reported by Kim *et al.* in Northern California.[321,334] The 2019/20 influenza season in the UK ended in late March.[335] Other UK cohorts recruited during the spring wave of COVID-19 (March - May 2020) similarly reported very little or no viral co-infection.[324,333]

8.4.3 Strengths and limitations

This pragmatic multicentre study provides novel data on both community-acquired and nosocomial co-infection/ co-colonisation in patients with COVID-19 requiring ICU care in England. The ICU cohort represents those with severe disease who were subject to more rigorous microbiology sampling.

A key limitation of the study is its retrospective observational design subject specifically to case selection, ascertainment and sampling biases. Inclusion of consecutive eligible patients was not feasible due to pandemic workload constraints. To minimise case selection bias, participating sites submitted a random sample of their eligible cohort, although random sampling methods were not standardised. The impact of ascertainment bias due to differences in the proportion of eligible cases submitted by each institution was reduced through the participation of multiple centres. The study cohort was comparable to the ICNARC cohort except for an under-representation of patients of Black, Asian and Minority Ethnicity (BAME). Our results may not be applicable to settings

with larger BAME populations. Restriction of our cohort to those with completed ICU admissions excluded: i) frailer patients in whom ICU care was deemed not appropriate, and ii) patients with very long ICU stays. Co-infection, particularly nosocomial infection, may be higher in these patients. A second key limitation is that although results likely to represent contamination were excluded, some pathogens found in respiratory tract samples may represent colonisation rather than active co-infection. However, as sputum samples sent from ICU should reflect clinical concern of lower respiratory tract infection (especially during the pandemic timeframe) and positive culture represents predominant presence of a pathogen rather than as part of mixed flora, we have taken these results to represent infection. If colonising pathogens were wrongly attributed as causing infection, the direction of bias would be towards falsely higher co-infection rates observed in our study. Thirdly, reliance on culture dependent techniques may have falsely decreased co-infection rates. Antibiotic use prior to admission was low (13.8%), increasing the reliability of culture-based methods on admission. However, detection of pathogens later into admission would have been influenced by sampling bias and the use of empirical antibiotics. Fourthly, although seven hospitals participated in this study, one study site contributed a third of cases; observed 48-hour co-infection/ co-colonisation rate excluding this site was, however, similar to overall results.

8.4.4 Implications for future work

Notwithstanding these limitations, our data indicate that early in hospitalisation, bacterial co-infection in COVID-19 is very uncommon and support the recommendations that empirical antibiotics should not be started routinely in primary care or at the point of hospital admission without clinical suspicion of bacterial infection.[307] The high rate of co-infection found late in illness among patients requiring ICU and involving nosocomial pathogens is concerning. It is plausible that reducing unnecessary early antibiotic

exposure in patients with COVID-19 could reduce their risk of late, Gram negative, potentially antibiotic resistant infections.[336,337]

Since study completion, dexamethasone has been shown to decrease mortality in patients hospitalised with COVID-19 who require oxygen support or invasive mechanical ventilation.[338] Consequently, dexamethasone has become established as standard of care for these patients in many countries. This may increase the already high rate of bacterial co-infection we observed in ICU-treated patients. A high level of microbiological vigilance is recommended as part of the management of these patients. In the setting of seasonal changes in respiratory pathogens, ongoing surveillance for co-infections in patients hospitalised with COVID-19, ideally through prospective studies with standardised sampling protocols, is advised.

Chapter 9

Chapter 9 Conclusion

9.1 Key findings

This thesis has investigated different aspects of morbidity after CAP and these are the key findings:

1. **Chapter 3:** A previously unrecognised large burden of morbidity during recovery from pneumonia was found, with almost 56% of patients consulting primary care within 30 days of hospital discharge. The highest rate of consultation occurred early, i.e. within 7 days. Nearly 40% of consultations were for a respiratory disorder and 30% of patients consulting received further antibiotics.
2. **Chapter 4:** The systematic review of 47 studies found in-hospital incidence of cardiac complications of 3.1% for ACS, 7.7% for heart failure and 7.9% for arrhythmia. The commonly reported risk factors include older age, severity of pneumonia and pre-existing cardiac disease. Patients who developed cardiac complications were approximately three times more likely to die both in-hospital and within 30 days of admission than those who did not.
3. **Chapter 5:** Compared to age, gender and practice-matched patients without pneumonia in the population-based study, those with pneumonia were significantly at higher risk of developing all cardiac complications, with the highest risk observed for developing arrhythmia at 30 days after discharge, and declining incidence at 90 days and 1 year.
4. **Chapter 6:** The systematic review of 27 studies found that current and ex-smokers were both significantly at higher risk of developing CAP whilst passive tobacco smoke exposure had a significant effect only in those aged ≥ 65. With current smokers, a dose-response trend with higher risk of CAP in those where higher amounts of tobacco was recorded.

5. **Chapter 7:** From the population-based study, 3.1% and 9.0% developed recurrent pneumonia within 90 days and 1 year of follow-up respectively. Current tobacco smoking status at index hospitalisation for pneumonia was independently associated with a higher risk of recurrent pneumonia. Only 40% of patients who smoke that were hospitalised with pneumonia received stop smoking interventions in the year before and even less with 30% in the year after admission for index pneumonia.
6. **Chapter 8:** Bacterial co-infection within 48 hours of hospital admission for COVID-19 infection in adults was uncommon; 1.6% on admission and 5.5% within 48 hours. The commonest pathogens identified within the first 48 hours of hospital admission were *S. aureus* and *S. pneumoniae.* The proportion of co-pathogens detected increased with duration of ICU stay and consisted largely of Gram-negative bacteria, particularly *Klebsiella pneumoniae* and *Escherichia coli*. Patients with co-infections were more likely to die in ICU (crude OR 1.78,95% CI 1.03-3.08, p=0.04) compared to those without co-infections.

9.2 Implications

Taken together, this thesis highlights that patients experience a significant morbidity during recovery from pneumonia. After discharge from hospital, patients often continue to report persistence of symptoms, including fatigue, cough and dyspnoea, associated with functional impairment for several weeks.[54] Previous studies have demonstrated that patients often lack a clear understanding about the short and long-term consequences of CAP, or the natural course of their symptoms.[95,96] Ongoing unaddressed patient needs may contribute towards the high level of primary care consultation observed as patients seek reassurance of adequate recovery. Such consultations may be avoidable. In the

context of current COVID-19 pandemic, 'long covid' is a term that is widely used to describe signs and symptoms which develop during or after a COVID-19 infection which persists for more than 12 weeks, without an alternative diagnosis.[339] Symptoms described are similar to that seen in CAP generally, irrespective of the causative pathogen including fatigue, cough and breathlessness.[101] Education of patients, the public, clinicians and policy makers regarding the sometimes prolonged morbidity associated with hospitalisation with pneumonia is necessary to support patient recovery.

This thesis has also provided a deeper insight into the importance of preventing or reducing considerable burden of morbidity that patients experience after pneumonia, with specific focus to cardiac complications after pneumonia and addressing tobacco smoking. Most cardiac complications occur within 30 days of hospitalisation for CAP, with declining rate at 90 days and subsequently a year after CAP. An individualized risk assessment would be useful to identify patients at risk in order to target measures for preventing the occurrence of cardiac complications. These may include provision of pneumococcal and influenza vaccination alongside potential adjunctive therapies as discussed in Chapter 5. A major concern noted in this thesis was that cardiac complications following CAP is associated with high risk of mortality. In view of this, a high index of suspicion for cardiac complications is needed; these patients should be promptly investigated and managed effectively to prevent the progression of the cardiac complications.

Tobacco smoking is associated with an increased risk of developing cardiovascular disease as well as pneumonia, with a well-described dose-dependent association.[205,206] This observation is further extended to an association between tobacco smoking, a modifiable risk factor and recurrent pneumonia. This highlights the importance of

implementing effective smoking cessation interventions, which include behavioural support, pharmacotherapy (bupropion, nicotine replacement therapy and varenicline) and very brief advice as a key component of pneumonia management, in accordance with the NHS Long Term Plan.[93,292]

Chapter 8 in this thesis raises a crucial issue on the management of critically ill patients with COVID-19 infection. A better understanding of the incidence of co-infection in these patients and the pathogens involved is necessary for effective antimicrobial stewardship. Only limited evidence for community-acquired bacterial co-infection was found, but there was a high rate of Gram-negative infection acquired during ICU stay. This study supports the recommendation that empirical antibiotics should not be started routinely in primary care or at the point of hospital admission without clinical suspicion of bacterial infection.[307] The high rate of co-infection found late in illness among patients requiring ICU and involving nosocomial pathogens is concerning. It is plausible that reducing unnecessary early antibiotic exposure in patients with COVID-19 could reduce their risk of late, Gram negative, potentially antibiotic resistant infections.[336,337]

9.3 Future research recommendations

Research in this thesis have identified that a lack of recognition of the burden of morbidity during recovery from pneumonia has thus far meant that evidence-based interventions to meet patients' needs have not been adequately developed. Future research should focus on developing targeted interventions to improve patients' knowledge of their condition and recovery, therefore empowering them to become more aware of when to seek medical attention, and in turn reducing avoidable healthcare consultations. A randomised controlled trial of targeted interventions such as providing

standardised patient information resource (for instance, in the form of written information leaflet, dedicated website, video, mobile app on its own or in combination), and patient support using telephone helpline by a dedicated pneumonia specialist nurse compared to 'usual care' would provide valuable information on the appropriate cost-effective measures that should be implemented to improve patient experience when diagnosed with pneumonia (**Table 9-1**). As part of this initiative, I have worked closely with the Graphic Design and Video Production team locally to design and complete the recording of a patient information video about pneumonia which has been uploaded to The Pneumonia Trust website (http://www.pneumoniatrust.co.uk). This video would be a useful resource for patients, families and healthcare professionals who want to obtain more information about what is pneumonia, the causes, prevention, diagnosis, treatment and recovery.

Table 9-1: A future study using PICO framework

Patients - Adults (≥18) hospitalised with community-acquired pneumonia (CAP)

Intervention – Randomised-controlled trial of enhanced nurse-led support, delivered by dedicated pneumonia specialist nurse versus usual care

- providing standardised patient information resource (for instance, in the form of written information leaflet, dedicated website, video, and mobile application) prior to discharge from hospital
- stop smoking interventions
- physiotherapy review
- active telephone contact at 7 days (unless otherwise stated by patient)
- passive helpline for patients to contact after discharge (up to 6 weeks)
- offer of face-to-face clinic visit if deemed necessary from telephone conversation.

Control - usual care which consist of verbal information

Outcome -

- Primary outcome measured at 6 weeks: healthcare utilisation rate (including primary care, urgent care, emergency department visits and hospital readmissions)
- Secondary outcomes measured at 6 weeks, 90 days and 1 year:
    - functional impairment: return to work, loss of independence, job loss
    - patient experience: change in patient reported outcome measure (CAP-symptom questionnaire), change in Hospital Anxiety and Depression Scale (HADS) score
    - smoking status
    - incidence of cardiac complications

The main difference in the suggested care pathway compared to current care is the provision of additional package of information and enhanced nurse-led support. The health economic cost would take into account the cost of employing a dedicated pneumonia specialist nurse, cost of telephone support, cost of running a drop-in clinic. There is a potential cost saving from reduction in healthcare resource utilisation (e.g., reduction in length of hospital stay, readmission and primary care, urgent care or emergency department visits) and sickness absence.

Deciding whether a consultation is warranted, or not, is a clinical decision that includes consideration of a range of factors including social, medical and behavioural factors. The current study in Chapter 3 provides the platform to design and conduct further studies that will address the many remaining unanswered questions in this field, including the proportion of post-discharge consultations that are warranted, how many and which consultations may be avoided and whether there are barriers to consultation (for those who should consult but do not). To accurately measure and assess the value of a consultation would ideally require a prospective study design that captures the opinion of the attending healthcare professional as well as collection of data relating to the full range of actions arising from a consultation, such as referral for an x-ray, secondary care consultation, other investigations, and input from other healthcare professionals.

Antibiotic use is associated with the development of antimicrobial resistance (AMR) which is acknowledged globally as a major threat to public and individual health. This is evidenced by the World Health Organisation (WHO)'s commitment to tackling AMR, the selection of AMR by the UK public as the challenge for the current "Longitude Prize", and the Department of Health's strategic paper on AMR.[340–342] With regards to antibiotic prescribing at post-discharge consultation, further studies are required to determine the reasons for antibiotic prescription at these consultations especially at the interface between primary and secondary care, and their appropriateness.

Most cardiac complications occur within 30 days of hospitalisation for CAP, with associated high mortality. There is yet a validated prediction tool that clinicians can easily use to identify patients who are at high risk of developing cardiac complications when hospitalised for CAP. This tool could include identified risk factors from this thesis such as age, gender, smoking status, pre-existing heart disease and potentially including cardiac biomarkers if more evidence becomes available. A change of approach in managing patients with pneumonia is warranted; although the identified risk factors are also intuitively the common risk factors for developing heart disease, unless a high index of suspicion for cardiac complications after pneumonia is present amongst treating physicians, these patients will not receive the optimum medical management. In addition, randomised controlled trials would be required to assess the role of vaccinations (pneumococcal and influenza) and potential adjunctive therapies such as statins, antiplatelet drugs and angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), in preventing the occurrence of cardiac complications.

As previously discussed, tobacco smoking is an important modifiable risk factor for developing index pneumonia, recurrent pneumonia and cardiac complications. Reassuringly, the risk is lower in ex-smokers. However, further research is warranted to establish why and for how long ex-smokers continue to be at higher risk following smoking cessation, compared to those who have never smoked. An extension to the study in Chapter 7 could potentially be to assess the risk of recurrent pneumonia in ex-smokers. In order to investigate this, a prospective study design is needed, documenting the conversion of current smokers on admission for index hospitalisation for pneumonia to ex-smokers on or after discharge. Data on change in smoking status can be collected using self-reported smoking status and validated by measuring exhaled carbon monoxide. The risk of recurrent CAP can be subsequently measured at 6-month or 12-month follow-up.[343]

Chalmers et al. concluded that pneumonia is an 'underestimated, neglected and underfunded' condition in the UK.[344] The COVID-19 pandemic has in many ways paved pathways to improve our understanding on morbidity after CAP. There is a surge in research worldwide assessing the long-term effects of COVID-19 or 'long covid'.[102] The Post-hospitalisation COVID-19 Study (PHOSP-COVID) in the UK aims to recruit 10, 000 patients, who will be followed-up for a year.[345] Similar studies assessing the long-term effects of pneumonia need to be conducted to better understand the associated morbidity.

9.4 Conclusion

In conclusion, this thesis highlights that patients experience a significant morbidity during recovery from pneumonia. Furthermore, a lack of recognition of the burden of morbidity

has thus far meant that evidence-based interventions to meet patients' needs have not been adequately developed. The COVID-19 pandemic has in many ways paved pathways to improve our understanding on the morbidity after CAP. The recognition of 'long covid' and the surge in current global research into assessing the long-term effects of COVID-19 may inform relevant interventions that could be applied to effectively reduce the morbidity and improve the long-term outcomes of patients recovering from pneumonia.

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Appendix

Appendix 1: ISAC Protocol

ISAC APPLICATION FORM
PROTOCOLS FOR RESEARCH USING THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

For ISAC use only		
Protocol No. Submission date (DD/MM/YYYY)	....	***IMPORTANT*** *Please refer to the **guidance** for '**Completing the ISAC application form'** found on the CPRD website (www.cprd.com/isac). If you have any queries, please contact the ISAC Secretariat at isac@cprd.com.*

SECTION A: GENERAL INFORMATION ABOUT THE PROPOSED RESEARCH STUDY

1. Study Title[§] (*Please state the study title below)*

Study of recovery in patients hospitalised with community acquired pneumonia using Clinical Practice Research Datalink (CPRD), linked to Hospital Episode Statistics.

[§]Please note: This information will be published on the CPRD's website as part of its transparency policy.

2. Has any part of this research proposal or a related proposal been previously submitted to ISAC?

Yes[*] ☐ No √

**If yes, please provide the previous protocol number/s below. Please also state in your current submission how this/these are related or relevant to this study.*

3. Has this protocol been peer reviewed by another Committee? (e.g. grant award or ethics committee)

Yes[*] ☐ No √

**If Yes, please state the name of the reviewing Committee(s) below and provide an outline of the review process and outcome as an Appendix to this protocol :*

4. Type of Study (please tick all the relevant boxes which apply)

Adverse Drug Reaction/Drug Safety	☐	Drug Effectiveness	☐
Drug Utilisation	√	Pharmacoeconomics	☐
Disease Epidemiology	√	Post-authorisation Safety	☐
Health care resource utilisation	√	Methodological Research	☐
Health/Public Health Services Research	☐	Other[*]	☐

[*]If Other, please specify the type of study here and in the lay summary below:

5. Health Outcomes to be Measured[§]

[§]Please note: This information will be published on CPRD's website as part of its transparency policy.

Please summarise below the primary/secondary health outcomes to be measured in this research protocol:

Primary outcomes

- Reconsultation rate following hospitalisation for CAP, stratified by time: within the first 7 days, 8- 14 days, 15- 30 days, 31- 60 days
- Causes of reconsultation; respiratory versus non-respiratory (cardiac, cognitive impacts)

- Antibiotic prescription rate at reconsultation

Secondary outcomes

- Types of antibiotics prescribed at reconsultation
- Association of antibiotic prescription at reconsultation with further reconsultation episodes within 30 days
- Assocation of reconsultation with underlying comorbid illnesses
- Incidence of incipient cognitive decline and cardiac disease following CAP at 30 days, 90 days and 1 year.
- To determine whether current smokers admitted with index pneumonia were given smoking cessation advice both before and after developing pneumonia
- To determine the rate of recurrent pneumonia by smoking status
- To determine the effect of tobacco smoking on hospitalisation for recurrence of pneumonia

6. Publication: This study is intended for (please tick all the relevant boxes which apply)**:**

Publication in peer-reviewed journals	√	Presentation at scientific conference	√
Presentation at company/institutional meetings	√	Regulatory purposes	☐
Other*	☐		

**If Other, please provide further information:*

SECTION B: INFORMATION ON INVESTIGATORS AND COLLABORATORS

7. Chief Investigator§

Please state the full name, job title, organisation name & e-mail address for correspondence - see guidance notes for eligibility. Please note that there can only be one Chief Investigator per protocol.

Tricia McKeever
Division of Epidemiology and Public Health
Clinical Sciences Building
Nottingham City Hospital
Tricia.McKeever@nottingham.ac.uk

§*Please note: The name and organisation of the Chief Investigator and will be published on CPRD's website as part of its transparency policy*

CV has been previously submitted to ISAC	√ **CV number: 655_16**
A new CV is being submitted with this protocol	☐
An updated CV is being submitted with this protocol	☐

8. Affiliation of Chief Investigator (full address)

Tricia McKeever
Division of Epidemiology and Public Health
Clinical Sciences Building
Nottingham City Hospital
Tricia.McKeever@nottingham.ac.uk

9. Corresponding Applicant§

Please state the full name, affiliation(s) and e-mail address below:

Dr Vadsala Baskaran
Nottingham University Hospitals NHS Trust
City Hospital Campus

Hucknall Road
Nottingham NG5 1PB
vadsala.baskaran@nhs.net

§*Please note: The name and organisation of the corresponding applicant and their organisation name will be published on CPRD's website as part of its transparency policy*

Same as chief investigator	☐	
CV has been previously submitted to ISAC	☐	**CV number:**
A new CV is being submitted with this protocol	√	
An updated CV is being submitted with this protocol	☐	

10. List of all investigators/collaborators§

Please list the full name, affiliation(s) and e-mail address* of all collaborators, other than the Chief Investigator below:

§*Please note: The name of all investigators and their organisations/institutions will be published on CPRD's website as part of its transparency policy*

Other investigator:

Professor Wei Shen Lim
Nottingham University Hospitals NHS Trust
City Hospital Campus
Hucknall Road
Nottingham NG5 1PB

CV has been previously submitted to ISAC	☐	**CV number:**
A new CV is being submitted with this protocol	√	
An updated CV is being submitted with this protocol	☐	

Other investigator:

CV has been previously submitted to ISAC	☐	**CV number:**
A new CV is being submitted with this protocol	☐	
An updated CV is being submitted with this protocol	☐	

Other investigator:

CV has been previously submitted to ISAC	☐	**CV number:**
A new CV is being submitted with this protocol	☐	
An updated CV is being submitted with this protocol	☐	

Other investigator:

CV has been previously submitted to ISAC	☐	**CV number:**
A new CV is being submitted with this protocol	☐	
An updated CV is being submitted with this protocol	☐	

[Please add more investigators as necessary]

Please note that your ISAC application form and protocol **must be copied to all e-mail addresses listed above at the time of submission of your application to the ISAC mailbox. Failure to do so will result in delays in the processing of your application.*

11. Conflict of interest statement*

Please provide a draft of the conflict (or competing) of interest (COI) statement that you intend to include in any publication which might result from this work

Each publication will acknowledge National Institute of Health Research (NIHR) Nottingham BRC as the study funder.
VB- received salary derived from NIHR Nottingham BRC
WSL- received grants from NIHR as well as investigator initiated unrestricted grant from

Pfizer.

**Please refer to the International Committee of Medical Journal Editors (ICMJE) for guidance on what constitutes a COI.*

12. Experience/expertise available

Please complete the following questions to indicate the experience/ expertise available within the team of investigators/collaborators actively involved in the proposed research, including the analysis of data and interpretation of results.

	Previous GPRD/CPRD Studies	**Publications using GPRD/CPRD data**
None	☐	☐
1-3	☐	☐
> 3	√	√

Experience/Expertise available	**Yes**	**No**
Is statistical expertise available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Tricia McKeever	√	☐
Is experience of handling large data sets (>1 million records) available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Tricia McKeever	√	☐
Is experience of practising in UK primary care available to or within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Tricia McKeever	√	☐

13. References relating to your study

Please list up to 3 references (most relevant) relating to your proposed study:

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 J R Coll Physicians London. 2018;18(1):41–6.

Millett ERC, 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).

Lim WS, Baudouin S V, 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 [Internet]. 2009;64(Suppl 3):iii1-iii55. Available from: http://thorax.bmj.com/cgi/doi/10.1136/thx.2009.121434

SECTION C: ACCESS TO THE DATA

14. Financial Sponsor of study[§]

[§]*Please note: The name of the source of funding will be published on CPRD's website as part of its transparency policy*

Pharmaceutical Industry	☐	*Please specify name and country*
Academia	√	*Please specify name and country: NIHR Nottingham BRC*
Government / NHS	☐	*Please specify name and country:*
Charity	☐	*Please specify name and country:*
Other	☐	*Please specify name and country:*
None	☐	

15. Type of Institution conducting the research

Pharmaceutical Industry	☐	*Please specify name and country:*
Academia	√	*Please specify name and country:* University of Nottingham
Government Department	☐	*Please specify name and country:*
Research Service Provider	☐	*Please specify name and country:*
NHS	☐	*Please specify name and country:*
Other	☐	*Please specify name and country:*

16. Data access arrangements

The financial sponsor/ collaborator* has a licence for CPRD GOLD and will extract the data
☐

The institution carrying out the analysis has a licence for CPRD GOLD and will extract the data**
√

A data set will be provided by the CPRD[¥€]
☐

CPRD has been commissioned to extract the data and perform the analyses[€]
☐

Other:
☐

If Other, please specify:

**Collaborators supplying data for this study must be named on the protocol as co-applicants.*
***If data sources other than CPRD GOLD are required, these will be supplied by CPRD*
[¥]*Please note that datasets provided by CPRD are limited in size; applicants should contact CPRD (enquiries@cprd.com) if a dataset of >300,000 patients is required.*
[€]*Investigators must discuss their request with a member of the CPRD Research team before submitting an ISAC application. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email (enquiries@cprd.com) to discuss your requirements. Please also state the name of CPRD Research team with whom you have discussed this request (provide the date of discussion and any relevant reference information):*

Name of CPRD Researcher Tarita Murray-Thomas Reference number (where available) -
Date of contact 8/2/18

17. Primary care data

Please specify which primary care data set(s) are required)
Vision only (Default for CPRD studies √ Both Vision and EMIS®* ☐
EMIS® only* ☐

Note: Vision and EMIS are different practice management systems. CPRD has traditionally collected data from Vision practice. Data collected from EMIS is currently under evaluation prior to wider release.
Investigators requiring the use of EMIS data **must discuss the study with a member of the CPRD Research team before submitting an ISAC application*

Please state the name of the CPRD Researcher with whom you have discussed your request for EMIS data:
Name of CPRD Researcher Reference number (where available) Date of contact

18. Site Location of Data

a) Processing location(s):

Location area - UK / EEA / Worldwide: UK

Organisation address: University of Nottingham, Nottingham, NG7 2RD

Note: Please enter the location details of where the data for this study will be used (processed).

b) Storage Location(s)

Location area - UK / EEA / Worldwide: UK

Organisation address: University of Nottingham, Nottingham, NG7 2RD

Note: Please enter the location details of where the data for this study will be stored.

Territory of analysis - UK / EEA / Worldwide: UK

Note: Please enter the details of where the data for this study will be analysed.

SECTION D: INFORMATION ON DATA LINKAGES

19. Does this protocol seek access to linked data

Yes* √ No☐ If No, please move to section E.

Research groups which have not previously accessed CPRD linked data resources **must discuss access to these resources with a member of the CPRD Research team, before submitting an ISAC application. Investigators requiring access to HES Accident and Emergency data, HES Diagnostic Imaging Dataset, PROMS data, the Pregnancy Register, Cancer Registration, SACT and CPES data and the Mental Health Services Data Set **must** also discuss this with a member of the CPRD Research team before submitting an ISAC application. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email enquiries@cprd.comto discuss your requirements **before** submitting your application.*

Please state the name of the CPRD Researcher with whom you have discussed your linkage request.

Name of CPRD Researcher Elizabeth Crellin Reference number (where available) Date of contact 10.07.2018

Please note that as part of the ISAC review of linkages, your protocol may be shared - in confidence - with a representative of the requested linked data set(s) and summary details may be shared - in confidence - with the Confidentiality Advisory Group of the Health Research Authority.

20. Please select the source(s) of linked data being requested§

§Please note: This information will be published on the CPRD's website as part of its transparency policy.

☒ ONS Death Registration Data
√ HES Admitted Patient Care
☐ HES Outpatient
☐ HES Accident and Emergency
☐ HES Diagnostic Imaging Dataset
☐ HES PROMS (Patient Reported
☐ NCRAS (National Cancer Registration and Analysis Serv
Cancer Registration Data *
☐ NCRAS Cancer Patient Experience Survey (CPES) data
☐ NCRAS Systemic Anti-Cancer Treatment (SACT) data*
☐ Mental Health Services Data Set (MHDS)

Outcomes Measure)**
☐ CPRD Mother Baby Link
☐ Pregnancy Register

☒ Practice Level Index of Multiple Deprivation (Standard)
☐ Practice Level Index of Multiple Deprivation (Bespoke)
☒ Patient Level Index of Multiple Deprivation***
☐ Patient Level Townsend Score ***

**Applicants seeking access to NCRAS data must complete a Cancer Dataset Agreement form (available from CPRD). This should be submitted to the ISAC as an appendix to your protocol. Please also note that applicants seeking access to cancer registry data must provide consent for publication of their study title and study institution on the UK Cancer Registry website.*
***Assessment of the quality of care delivered to NHS patients in England undergoing four procedures: hip replacement, knee replacement, groin hernia and varicose veins. Please note that patient level PROMS data are only available for non-commercial purposes, such as academic research, or in connection with delivering services to the NHS.*
**** 'Patient level IMD and Townsend scores will not be supplied for the same study*
*****If "Other" is specified, please provide the name of the individual in the CPRD Research team with whom this linkage has been discussed.*

Name of CPRD Researcher Elizabeth Crellin Reference number (where available)
Date of contact 10.07.2018

21. Total number of linked datasets requested including CPRD GOLD

Number of linked datasets requested (*practice/ 'patient' level Index of Multiple Deprivation, Townsend Score, the CPRD Mother Baby Link and the Pregnancy Register should **not** be included in this count)* 2

Please note: Where ≥5 linked datasets are requested, approval may be required from the Confidentiality Advisory Group (CAG) to access these data

22. Is linkage to a local¥ dataset with <1 million patients being requested?

Yes* ☐ No √

**If yes, please provide further details:*
¥ Data from defined geographical areas i.e. non-national datasets.

23. If you have requested one or more linked data sets, please indicate whether the Chief Investigator or any of the collaborators listed in question 5 above, have access to these data in a patient identifiable form (e.g. full date of birth, NHS number, patient post code), or associated with an identifiable patient index.
Yes* ☐ No √

** If yes, please provide further details:*

24. Does this study involve linking to patient *identifiable* data (e.g. hold date of birth, NHS number, patient post code) from other sources?
Yes ☐ No √

SECTION E: VALIDATION/VERIFICATION

25. Does this protocol describe a purely observational study using CPRD data?

Yes* √ No** ☐

** Yes: If you will be using data obtained from the CPRD Group, this study does not require separate ethics approval from an NHS Research Ethics Committee.*
*** No: You may need to seek separate ethics approval from an NHS Research Ethics Committee for this study. The ISAC will provide advice on whether this may be needed.*

26. Does this protocol involve requesting any additional information from GPs?

Yes* ☐ No √

** If yes, please indicate what will be required:*

Completion of questionnaires by the GP[ψ] Yes ☐ No ☐
Is the questionnaire a validated instrument? Yes ☐ No ☐
If yes, has permission been obtained to use the instrument? Yes ☐ No ☐
Please provide further information:

Other (please describe)

[ψ] Any questionnaire for completion by GPs or other health care professional must be approved by ISAC before circulation for completion.

27. Does this study require contact with patients in order for them to complete a questionnaire?

Yes* ☐ No √

**Please note that any questionnaire for completion by patients must be approved by ISAC before circulation for completion.*

28. Does this study require contact with patients in order to collect a sample?

Yes* ☐ No √

** Please state what will be collected:*

SECTION F: DECLARATION

29. Signature from the Chief Investigator

- I have read the guidance on '***Completion of the ISAC application form****'* and '***Contents of CPRD ISAC Research Protocols***' and have understood these;
- I have read the submitted version of this research protocol, including all supporting documents, and confirm that these are accurate.
- I am suitably qualified and experienced to perform and/or supervise the research study proposed.
- I agree to conduct or supervise the study described in accordance with the relevant, current protocol
- I agree to abide by all ethical, legal and scientific guidelines that relate to access and use of CPRD data for research
- I understand that the details provided in sections marked with (§) in the application form and protocol will be published on the CPRD website in line with CPRD's transparency policy.
- I agree to inform the CPRD of the final outcome of the research study: publication, prolonged delay, completion or termination of the study.

Name: Prof Tricia McKeever Date: e-Signature (type name):Prof Tricia McKeever

PROTOCOL INFORMATION REQUIRED

The following sections below **must** be included in the CPRD ISAC research protocol. Please refer to the guidance on '***Contents of CPRD ISAC Research Protocols***' (www.cprd.com/isac) for more information on how to complete the sections below. Pages should be numbered. All abbreviations must be defined on first use.

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

A. Study Title[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

Study of recovery in patients hospitalised with community acquired pneumonia using Clinical Practice Research Datalink (CPRD), linked to Hospital Episode Statistics.

B. Lay Summary (Max. 200 words)[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

Community acquired pneumonia (CAP) is a common condition. Each year in the UK, over 100,000 adults are hospitalised because of CAP. Most (85 % - 90%) survive and are discharged after an average hospital stay of 7 days. Following discharge, patients report slow recovery lasting many weeks (~50% still have symptoms at 4 weeks). Some develop new heart problems. Many (>60%) reconsult their GPs after discharge, and a third receive more antibiotics.

The frequency at which post-discharge complications and reconsultation occurs are poorly described. Who suffers most and why are not understood. We propose using data from the Clinical Practice Research Datalink linked to Hospital Episode Statistics to determine the:

- frequency of reconsultation following a hospitalisation with CAP and the reasons thereof
- frequency and type of antibiotic prescription at reconsultation
- frequency of new heart and memory problems in the months following hospitalisation.

We will investigate who is more likely to develop problems during recovery from CAP, what those problems are and why these problems develop. We will also explore the value of additional antibiotic use after hospital treatment. These findings will aid identification of strategies to improve the care of patients recovering from CAP.

C. Technical Summary (Max. 200 words)[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

Objectives

To determine the incidence and reasons for reconsultation following hospitalisation with CAP, including antibiotic usage at reconsultation.

Methods

Adults with a first episode of hospitalised CAP between July 2002- June 2017 as recorded in CPRD linked to HES based on ICD-10 codes (J12- J18) will be included.

Data analysis

Statistical analyses will be performed using Stata 15. Incidence of CAP and other diseases (cognitive decline and cardiac complications) following CAP will be estimated using the whole CPRD as the denominator population. Incidence rates per 100,000 person-years,

adjusted incidence rate ratios and 95% confidence intervals will be described.

The independent association between patient characteristics and rate of reconsultation (overall/ patients without co-morbidities /patients with underlying respiratory disease) will be calculated using a multivariate logistic regression model; adjusted for age, gender, smoking, social deprivation, co-morbidities, vaccine status, length of hospital stay and intensive care unit admission. Causes of reconsultation will be divided into either respiratory or non-respiratory (cardiac symptoms and cognitive decline) symptoms.

We will measure the number of antibiotic prescriptions at reconsultation and where possible, the type of antibiotics prescribed. Association of antibiotic prescription at reconsultation with further reconsultation episodes will also be analysed.

D. Objectives, Specific Aims and Rationale

Objectives

To understand the morbidity of community acquired pneumonia following hospital discharge

Specific Aims

- To determine the rate of reconsultation following hospitalisation for CAP
- To determine the cause(s) of reconsultation
- To determine the number and type of antibiotic prescriptions at reconsultation
- To explore whether antibiotic prescription at reconsultation is associated with further reconsultation episodes.
- To investigate the association between reconsultation rate and underlying co-morbid diseases.
- To investigate the medium and longer-term extra-pulmonary impacts of CAP by determining the incidence of incipient cognitive decline and cardiac disease at 30 days, 90 days and 1 year after hospitalisation for CAP.

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Rationale

Patients report a high level of morbidity in the weeks following hospital treatment for CAP. However, there is almost no evidence-base to guide the management of patients post-discharge. Reconsultation and additional antibiotic use is common though their appropriateness is unknown. The CPRD-HES dataset provides a valuable means to close this evidence gap. The findings from this study will provide the grounding needed for the identification and development of interventions with the ultimate aim of reducing patient morbidity and healthcare resource utilisation.

E. Study Background

Lower respiratory tract infections (LRTIs) were reported as the 'most deadly communicable disease' worldwide in 2015, causing 3.2 million deaths.[27] It is the second commonest cause of death globally after ischaemic heart disease.[346] LRTI is a common diagnosis seen by primary care general practitioners, covering a spectrum of disease ranging from acute bronchitis to severe community acquired pneumonia (CAP). Community acquired pneumonia accounts for 5- 12% of LRTIs presenting to general practitioners.[23] Of these, 22- 42% are referred to hospital for further management.[3] Every year, over 100 000 patients with CAP are admitted to hospital in the UK.[97,347]

There is paucity of information on the recovery phase of CAP. Previous studies have

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*'
shown that between 35-86.5% of patients report at least one-CAP related symptom 30 days following radiographic evidence of pneumonia. [29,348] In a study of pneumococcal pneumonia, the symptoms that persisted were cough, dyspnoea, sputum production, pleuritic chest pain and fatigue[349]. The effect of prolonged symptom persistence during recovery on healthcare utilisation is not fully explored. In a study by Daniel et al, 65.7% of working age adults (18-65) reconsulted healthcare services within 28 days of discharge from hospital; 90.1% of these patients consulted their GP within 2 weeks of hospital discharge and 37% received further antibiotics.[47] Patients with CAP have been shown to develop new-onset cognitive impairment in both young and old adult patients.[350] Significant cardiac complications occur in patients within 30 days of CAP diagnosis.[159]
F. Study Type This study is primarily descriptive and hypothesis generating. We will explore the epidemiology of hospitalised CAP, healthcare resource utilisation/ reconsultations at both primary and secondary care and usage of further antibiotics at reconsultations. The association between reconsultation and potential explanatory factors (patient characteristics, comorbid diseases) will be investigated. We will also explore the value of antibiotics prescribed at reconsultation.
G. Study Design Cohort study
H. Feasibility counts A similar study conducted by Millett et al had a population size of 1,534,443 with 916,128 HES-linked patients.[77] This cohort of patients were used to calculate incidence of CAP.
I. Sample size considerations There is no formal power calculation for this study as we will use the entire population that meet the eligibility criteria listed in section K for our study. As mentioned in the previous section, a similar study conducted by Millett et al had a population size of 1,534,443 with 916,128 HES-linked patients.[77] Therefore it is estimated that we would have about 900,000 in our study.
J. Data Linkage Required (if applicable):[§] [§]*Please note that the data linkage/s requested in research protocols will be published by the CPRD as part of its transparency policy* CPRD data linked to HES Admitted Patient Care and HES Accident and Emergency will be used to determine the proportion of patients who are hospitalised for CAP. We will also be able to identify the proportion of patients who reconsult healthcare professionals (i.e. GPs or hospital doctors) after being discharged from hospital with CAP.

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

K. Study population

Only permanently registered acceptable patients and 'up-to-standard' follow-up will be included for the study. All patients with first episode of hospitalised CAP recorded in CPRD linked to HES Admitted Patient Care between 1st of July 2002 to 30th of June 2017 will be included. Information on the rate and cause for reconsultation as well as further antibiotic prescription at different time frames (i.e. within the first 7 days, 8- 14 days, 15-30 days, 31- 60 days) will be examined.

Inclusion criteria:
Adults aged > 18 with ICD-10 codes (J12- J18) for hospitalised CAP as documented in Appendix A

Exclusion criteria:

- Hospital admission in the preceding 10 days; identified either by CPRD hospital code or HES-linked data (ICD 10 code: Y95) which shows admission for any illness.
- Active tuberculosis

Index date is defined as the day of CAP diagnosed in hospital. All patients will be followed up from the index date to the end of data collection (1 year), date of transfer out of the practice or patient's death, whichever came first.

L. Selection of comparison group(s) or controls

Not applicable

M. Exposures, Health Outcomes[§] and Covariates

[§]*Please note: Summary information on health outcomes (as included on the ISAC application form above)will be published on CPRD's website as part of its transparency policy*

Exposures/ Outcomes:
Record of a ICD-10 code (J12- J18) for community acquired pneumonia as listed in Appendix A, and documented in the patient clinical or referral record will be used.

Data Sources:
Data sources for this study will include primary care clinical records, prescription drug files and HES linked data to hospital admissions and emergency department attendances.

Covariates:
Covariates that will be considered in this study include age, gender, smoking, social deprivation, co-morbidities, vaccine status, length of hospital stay and intensive care unit admission.

N. Data/ Statistical Analysis

Statistical analyses will be performed using Stata 15. Incidence of CAP and other diseases (cardiac complications and cognitive decline) will be estimated using the whole CPRD as the denominator population. Incidence rates (IR) per 100,000 person-years, adjusted

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*'
incidence rate ratios (IRR) and 95% confidence intervals (CIs) will be described. Baseline demographics and co-morbid diseases of adults who reconsulted will be compared to those who did not reconsult. The independent association between patient characteristics and rate of reconsultation (overall/ patients without co-morbidities /patients with underlying respiratory disease) will be calculated using a multivariable logistic regression model; adjusted for age, gender, smoking, social deprivation, the presence of co-morbidities (Charlson co-morbidity index), vaccine status, length of hospital stay and intensive care unit admission. The included variables in the final model will be those associated with healthcare reconsultation during univariate analysis. Cause of reconsultation will be divided into either 'CAP-related' (respiratory symptoms) or 'not CAP-related' (cardiac symptoms and cognitive decline). We will measure the number of antibiotic prescriptions at reconsultation and where possible, the type of antibiotics prescribed.
O. Plan for addressing confounding Study will be adjusted for confounding factors such as age, gender, smoking, social deprivation, co-morbidities, vaccine status, length of hospital stay and intensive care unit admission using multivariable logistic regression model.
P. Plans for addressing missing data The potential for missing data, particularly on covariates such as smoking and vaccine status may not be documented. This will be reported and recognised as a potential limitation.
Q. Patient or user group involvement (if applicable) Not applicable
R. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication **S.** All data arising from this study will be owned by University of Nottingham. On completion of the study, the data will be analysed, tabulated and a Final Study Report will be prepared which will be accessible via the Chief Investigator. The study protocol, full study report, anonymised participant level dataset, and statistical code for generating the results will be made publicly available. Manuscripts resulting from the research will be conceived, written, and published at the discretion of the Chief Investigator, and other members of the research team as appropriate. This activity will be independent from the Research Funder, who will not have any control over the content or results of any publications. It is anticipated that the research will lead to publications in subject-specific international peer-reviewed journals and presentations at international conferences.
T. Limitations of the study design, data sources, and analytic methods This large, population based study will be generalisable given that it will include approximately 900, 000 patients in the United Kingdom with linked data to hospital

admission and attendances to the emergency department. The cohort of patients in this study will be representative of the UK population with reference to age, gender and ethnicity. [351]

Information gathered in this study is deduced from the code sets used in CPRD, HES Admitted Patient Care and HES Accident and Emergency. Therefore it is recognised that the study assumes that the healthcare professionals have used the most accurate code set at each patient visit, accepting that there may be variations in coding of the disease between healthcare professionals.

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List of Appendices *(Submit all appendices as separate documents to this application)*
Amendment (21/08/2020) **Changes in Part 2:** Section C: **Technical Summary (Max. 200 words)**[§] Original statement: **Data analysis (paragraph 2)** The independent association between patient characteristics and rate of reconsultation (overall/ patients without co-morbidities /patients with underlying respiratory disease) will be calculated using a multivariate logistic regression model; adjusted for age, gender, smoking, social deprivation, co-morbidities, vaccine status, length of hospital stay and intensive care unit admission. Causes of reconsultation will be divided into either respiratory or non-respiratory (cardiac symptoms and cognitive decline) symptoms. We will measure the number of antibiotic prescriptions at reconsultation and where possible, the type of antibiotics prescribed. Association of antibiotic prescription at reconsultation with further reconsultation episodes will also be analysed. Amended statement: The independent association between patient characteristics and rate of reconsultation (overall/ patients without co-morbidities /patients with underlying respiratory disease) will be calculated using a competing-risks regression with death and readmission as competing events; adjusted for age, gender, smoking, alcohol consumption, practice region, primary care consultation in the previous year, social deprivation, co-morbidities, vaccine status, length of hospital stay, and admission year. Causes of reconsultation will be divided into either respiratory or non-respiratory (cardiac symptoms and cognitive decline) symptoms. We will measure the number of antibiotic prescriptions at reconsultation and where possible, the type of antibiotics prescribed. Association of antibiotic prescription at reconsultation with further reconsultation episodes will also be analysed. Proportion of patients who received smoking cessation advice before and after the index pneumonia episode will be calculated. The rate of pneumonia recurrence (per 100

person-years) will be determined by smoking status. Effect of smoking on hospitalization for recurrence of pneumonia will be determined using competing-risks regression (death as a competing event), adjusted for variables determined using directed acyclic graph (DAG).

Section D: **Objectives, Specific Aims and Rationale**

Original statement:

Specific Aims

Amended statement: (Addendum to **Specific Aims** subheading)

- To determine whether current smokers admitted with pneumonia were given smoking cessation advice both before and after developing pneumonia
- To determine the rate of pneumonia recurrence by smoking status
- To determine the effect of tobacco smoking on hospitalisation for recurrence of pneumonia

Section M: **Exposures, Health Outcomes§ and Covariates**

Addendum to **Exposures/ Outcomes:**

Primary care reconsultation was considered to have occurred if medical Read codes were recorded after the date of discharge from hospital; administration-related codes were excluded to capture face-to-face consultations.[74,75] If there were multiple Read codes recorded in a day per patient, this was counted as a single episode of consultation.

Smoking cessation advice/stop smoking interventions will be assessed using Read codes within CPRD. These Read code list will be developed using a combination of validated medical Read codes and product Read codes under British National Formulary (BNF) listing of "Drugs used in substance dependence: Nicotine dependence".[70,76]

'Recurrent pneumonia' was defined as hospitalisation with pneumonia 30 days after the index admission for pneumonia, identified using ICD-10 codes (J12-J18).

Covariates:

Original statement:

Covariates that will be considered in this study include age, gender, smoking, social deprivation, co-morbidities, vaccine status, length of hospital stay and intensive care unit admission.

Amended statement:

Covariates that will be considered in this study include age, gender, smoking, alcohol consumption, practice region, primary care consultation in the previous year, social deprivation, co-morbidities, vaccine status, length of hospital stay, and admission year. Validated codelists were used for pneumonia, smoking status, alcohol consumption, Charlson Comorbidity Index and specific co-morbidities of interest.[70,76,77]

Section N : **Data/ Statistical Analysis**

Original statement:

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*'
Statistical analyses will be performed using Stata 15. Incidence of CAP and other diseases (cardiac complications and cognitive decline) will be estimated using the whole CPRD as the denominator population. Incidence rates (IR) per 100,000 person-years, adjusted incidence rate ratios (IRR) and 95% confidence intervals (CIs) will be described. Baseline demographics and co-morbid diseases of adults who reconsulted will be compared to those who did not reconsult. The independent association between patient characteristics and rate of reconsultation (overall/ patients without co-morbidities /patients with underlying respiratory disease) will be calculated using a multivariable logistic regression model; adjusted for age, gender, smoking, social deprivation, the presence of co-morbidities (Charlson co-morbidity index), vaccine status, length of hospital stay and intensive care unit admission. The included variables in the final model will be those associated with healthcare reconsultation during univariate analysis. Cause of reconsultation will be divided into either 'CAP-related' (respiratory symptoms) or 'not CAP-related' (cardiac symptoms and cognitive decline). We will measure the number of antibiotic prescriptions at reconsultation and where possible, the type of antibiotics prescribed. Amended statement: Statistical analyses will be performed using Stata 15. Incidence of CAP and other diseases (cardiac disease and cognitive decline) will be estimated using the whole CPRD as the denominator population. Incidence rates (IR) per 100,000 person-years, adjusted incidence rate ratios (IRR) and 95% confidence intervals (CIs) will be described. For the estimation of cardiac disease, we will also calculate the incidence in age, sex and GP practice matched population to that of CAP to compare the incidence the rate of cardiac disease after CAP vs the general population. The independent association between patient characteristics and rate of reconsultation (overall/ patients without co-morbidities /patients with underlying respiratory disease) will be calculated using a competing-risks regression with death and readmission as competing events; adjusted for age, gender, smoking, alcohol consumption, practice region, primary care consultation in the previous year, social deprivation, co-morbidities, vaccine status, length of hospital stay, and admission year. Causes of reconsultation will be divided into either respiratory or non-respiratory (cardiac symptoms and cognitive decline) symptoms. We will measure the number of antibiotic prescriptions at reconsultation and where possible, the type of antibiotics prescribed. Association of antibiotic prescription at reconsultation with further reconsultation episodes will also be analysed. Proportion of patients who received smoking cessation advice before and after the index pneumonia episode will be calculated. The rate of pneumonia recurrence (per 100 person-years) will be determined by smoking status. Effect of smoking on hospitalization for recurrence of pneumonia will be determined using competing-risks regression (death as a competing event), adjusted for variables determined using directed acyclic graph (DAG). Competing-risks regression was chosen instead of multivariate logistic regression as it

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*'
takes into account any reconsultation before death or readmission in the former analysis whilst the latter does not. This given a more accurate results of the outcome of interest, for both reconsultation in primary care and recurrent pneumonia hospitalisation. Section O : **Plan for addressing confounding** Original statement: Study will be adjusted for confounding factors such as age, gender, smoking, social deprivation, co-morbidities, vaccine status, length of hospital stay and intensive care unit admission using multivariable logistic regression model. Amended statement: Study will be adjusted for confounding factors such as age, gender, smoking, alcohol consumption, practice region, primary care consultation in the previous year, social deprivation, co-morbidities, vaccine status, length of hospital stay, and admission year using competing-risks regression Directed acyclic graph (DAG) will used to identify the minimum set of confounders to close the back-door paths to address the objective of determining the effect of smoking on the risk of recurrent pneumonia. Section P: **Plans for addressing missing data** Original statement: The potential for missing data, particularly on covariates such as smoking and vaccine status may not be documented. This will be reported and recognised as a potential limitation. Amended statement: There may be missing data, particularly on covariates such as smoking status and alcohol consumption. If there were >3% missing data, we will use multiple imputation with chained equations to handle the missing data.

Appendix 2: Read codes

Comorbidities

Chronic pulmonary disease

Medcode	Description
105420	Asthma self-management plan review
38146	Asthma disturbs sleep weekly
233	Severe asthma attack
102209	Mini asthma quality of life questionnaire
100509	Under care of asthma specialist nurse
78	Asthma
103998	Asthma limits activities most days
73522	Work aggravated asthma
103612	Asthma never causes night symptoms
21232	Allergic asthma nec
102713	Asthma limits activities 1 to 2 times per month
13065	Moderate asthma
4606	Exercise induced asthma
26503	Asthma causes daytime symptoms most days
10043	Asthma annual review
9552	Change in asthma management plan
3366	Severe asthma
105674	Asthma self-management plan agreed
102400	Asthma causes night time symptoms 1 to 2 times per week
19519	Asthma treatment compliance unsatisfactory
107167	Number days absent from school due to asthma in past 6 month
5267	Intrinsic asthma
93353	Sequoiosis (red-cedar asthma)
13176	Asthma follow-up
106805	Chronic asthma with fixed airflow obstruction
16070	Asthma nos
45782	Extrinsic asthma nos
98185	Asthma control test
9663	Step up change in asthma management plan
100397	Asthma control questionnaire
24479	Emergency asthma admission since last appointment
102952	Asthma trigger - warm air
102341	Asthma trigger - pollen
18224	Asthma control step 3
3458	Occasional asthma
185	Acute exacerbation of asthma
103813	Asthma trigger - cold air
40823	Brittle asthma
2290	Allergic asthma
26501	Asthma never causes daytime symptoms
39570	Asthma causes night symptoms 1 to 2 times per month
102449	Asthma trigger - respiratory infection
58196	Intrinsic asthma with status asthmaticus
102888	Asthma limits activities 1 to 2 times per week
26861	Asthma sometimes restricts exercise
45073	Intrinsic asthma nos

8335	Asthma attack nos
9018	Number of asthma exacerbations in past year
7731	Pollen asthma
93736	Royal college of physicians asthma assessment
25791	Asthma clinical management plan
16785	Asthma control step 1
5627	Hay fever with asthma
13064	Asthma severity
7058	Emergency admission, asthma
38144	Asthma limits walking up hills or stairs
103955	Asthma trigger - tobacco smoke
6707	Extrinsic asthma with asthma attack
4892	Status asthmaticus nos
10487	Asthma - currently active
39478	Wood asthma
31167	Asthma night-time symptoms
38145	Asthma limits walking on the flat
3665	Late onset asthma
12987	Late-onset asthma
5867	Exercise induced asthma
103945	Asthma trigger - damp
103318	Health education - structured patient focused asthma discuss
103952	Asthma trigger - emotion
1555	Bronchial asthma
19520	Asthma treatment compliance satisfactory
7146	Extrinsic (atopic) asthma
10274	Asthma medication review
8355	Asthma monitored
15248	Hay fever with asthma
26504	Asthma never restricts exercise
7378	Asthma management plan given
24884	Asthma causes daytime symptoms 1 to 2 times per week
20886	Asthma control step 4
102170	Asthma review using roy colleg of physicians three questions
100740	Health education - structured asthma discussion
3018	Mild asthma
47337	Asthma accident and emergency attendance since last visit
16667	Asthma control step 2
232	Asthma attack
102395	Asthma causes symptoms most nights
46529	Attends asthma monitoring
30458	Asthma monitoring by doctor
81	Asthma monitoring
29325	Intrinsic asthma without status asthmaticus
103631	Royal college physician asthma assessment 3 question score
100107	Health education - asthma self management
41017	Aspirin induced asthma
4442	Asthma unspecified
7416	Asthma disturbing sleep
31225	Asthma causes daytime symptoms 1 to 2 times per month
38143	Asthma never disturbs sleep
18323	Intrinsic asthma with asthma attack
26506	Asthma severely restricts exercise
102871	Asthma trigger - exercise
25181	Asthma restricts exercise
18223	Step down change in asthma management plan

42824	Asthma daytime symptoms
102301	Asthma trigger - seasonal
47684	Detergent asthma
103321	Asthma trigger - animals
19167	Asthma monitoring by nurse
41020	Absent from work or school due to asthma
30815	Asthma causing night waking
13175	Asthma disturbs sleep frequently
103944	Asthma trigger - airborne dust
14777	Extrinsic asthma without status asthmaticus
22752	Occupational asthma
24506	Further asthma - drug prevent.
27926	Extrinsic asthma with status asthmaticus
99793	Patient has a written asthma personal action plan
7191	Asthma limiting activities
11370	Asthma confirmed
20860	Asthma control step 5
45771	Chronic obstructive pulmonary disease does not disturb sleep
15626	Chronic catarrhal bronchitis
18476	Copd follow-up
3243	Chronic bronchitis
40788	Other emphysema
64721	Chronic emphysema due to chemical fumes
11150	Mucopurulent chronic bronchitis
38074	Chronic obstructive pulmonary disease monitor phone invite
104608	End stage chronic obstructive airways disease
67040	Other specified chronic obstructive pulmonary disease
106945	Chronic obstructive pulmonary disease rescue pack declined
66043	Other chronic bronchitis
34202	Chronic obstructive pulmonary disease monitoring 2nd letter
65733	[x]other specified chronic obstructive pulmonary disease
9520	Chronic obstructive pulmonary disease monitoring
794	Emphysema
45089	Chronic tracheobronchitis
37959	Fetid chronic bronchitis
34215	Chronic obstructive pulmonary disease monitoring 3rd letter
37371	Chronic obstructive pulmonary disease monitoring due
42313	Health education - chronic obstructive pulmonary disease
70787	Atrophic (senile) emphysema
66058	[x]other emphysema
56860	Segmental bullous emphysema
5909	Chronic wheezy bronchitis
99536	Bullous emphysema with collapse
26018	Chronic obstructive pulmonary disease monitoring by nurse
16410	Other emphysema nos
7884	Chronic obstructive pulmonary disease with acute exacerbation, unspecified
42258	Chronic obstructive pulmonary disease monitoring verb invite
33450	Emphysema nos
44525	Obstructive chronic bronchitis nos
5710	Chronic obstructive airways disease nos
10802	Moderate chronic obstructive pulmonary disease
10980	Centrilobular emphysema
104985	On chronic obstructive pulmonary disease supprtv cre pathway
998	Chronic obstructive airways disease
1001	Chronic obstructive pulmonary disease
26306	Chronic bullous emphysema

68662	Zonal bullous emphysema
61513	Mucopurulent chronic bronchitis nos
5798	Chronic asthmatic bronchitis
11287	Chronic obstructive pulmonary disease annual review
9876	Severe chronic obstructive pulmonary disease
68066	Other chronic bronchitis nos
103494	History of chronic obstructive pulmonary disease
102685	Chronic obstructive pulmonary disease 3 monthly review
18621	Chronic obstructive pulmonary disease follow-up
104481	Has chronic obstructive pulmonary disease care plan
61118	Simple chronic bronchitis nos
93568	Very severe chronic obstructive pulmonary disease
46578	Panlobular emphysema
25603	Simple chronic bronchitis
10863	Mild chronic obstructive pulmonary disease
45770	Chronic obstructive pulmonary disease disturbs sleep
7092	Recurrent wheezy bronchitis
109774	Telehealth chronic obstructive pulmonary disease monitoring
23492	Chronic bullous emphysema nos
15157	Chronic bronchitis nos
18792	Chronic obstructive pulmonary disease monitoring admin
105457	Chronic obstructive pulmonary disease care pathway
45998	Chronic obstructive pulmonary disease monitoring by doctor
45777	Chronic obstructive pulmonary disease clini management plan
60188	Giant bullous emphysema
24248	Mixed simple and mucopurulent chronic bronchitis
14798	Emphysematous bronchitis
12166	Other specified chronic obstructive airways disease
28755	Chronic obstructive pulmonary disease monitoring 1st letter
1446	Acute exacerbation of chronic obstructive airways disease
106637	Seen in chronic obstructive pulmonary disease clinic
37247	Chronic obstructive pulmonary disease nos
40159	Purulent chronic bronchitis
21061	Chronic obstructive pulmonary disease with acute lower respiratory infection
103007	Chronic obstructive pulmonary disease 6 monthly review
27819	Obstructive chronic bronchitis
101042	Issue of chronic obstructive pulmonary disease rescue pack
41491	Post-infective bronchiectasis
2195	Bronchiectasis
109816	H/o: bronchiectasis
15693	Tuberculous bronchiectasis
20364	Recurrent bronchiectasis
56427	Congenital bronchiectasis
32679	Bronchiectasis nos
62442	Allergic extrinsic alveolitis nos
63174	Hamman - rich syndrome
51410	Asbestosis nos
31423	Pneumoconiosis nos
46460	Silica and silicate pneumoconiosis
65376	Pneumoconiosis due to other inorganic dust
47718	Myositis in sarcoidosis
4084	Airways obstructn irreversible
103559	Usual interstitial pneumonitis
7791	Postinflammatory pulmonary fibrosis
8303	Asbestosis
73284	[x]sarcoidosis of other and combined sites

51858	Other allergic alveolitis
8317	Interstitial lung disease nec
34437	Sarcoid myocarditis
23461	Pneumoconiosis due to inorganic dust nos
52519	Myopathy due to sarcoidosis
55552	Other allergic alveolitis nos
28853	Fibrosing alveolitis associated with rheumatoid arthritis
6051	Diffuse pulmonary fibrosis
65060	[x]other interstitial pulmonary diseases with fibrosis
47037	Sarcoid heart disease
91912	[x]other specified interstitial pulmonary diseases
53095	Allergic alveolitis and pneumonitis nos
55612	Multiple cranial nerve palsies in sarcoidosis
49454	Meningitis due to sarcoidosis
49075	Sarcoidosis of lymph nodes
28229	Idiopathic fibrosing alveolitis nos
40613	Sarcoid arthropathy
103753	Idiopathic pulmonary fibrosis
5519	Cryptogenic fibrosing alveolitis
105939	[x]pneumoconiosis due to other dust containing silica
6837	Idiopathic fibrosing alveolitis
46977	Allergic alveolitis and pneumonitis nos
25013	Pneumoconioses
26405	Hepatic granulomas in sarcoidosis
3865	Sarcoidosis
11312	Extrinsic allergic alveolitis
103472	Pulmonary fibrosis
23446	Silica pneumoconiosis nos
3859	Pulmonary sarcoidosis
60805	Talc pneumoconiosis
27769	Sarcoidosis of skin
58841	Sarcoidosis of lung with sarcoidosis of lymph nodes
72595	Sarcoidosis of inferior turbinates
33980	Sarcoidosis of lung
19492	Coal workers' pneumoconiosis
40751	Polyneuropathy in sarcoidosis

Myocardial infarction

Medcode	Description
96838	[x]acute transmural myocardial infarction of unspecif site
109035	[x]subsequent myocardial infarction of other sites
99991	[x]subsequent myocardial infarction of unspecified site
40429	Acute anteroapical infarction
12139	Acute anterolateral infarction
17872	Acute anteroseptal infarction
28736	Acute atrial infarction
9276	Acute coronary insufficiency
11983	Acute coronary syndrome
8935	Acute inferolateral infarction
29643	Acute inferoposterior infarction
241	Acute myocardial infarction
14658	Acute myocardial infarction nos
9507	Acute non-q wave infarction
10562	Acute non-st segment elevation myocardial infarction
62626	Acute papillary muscle infarction
32854	Acute posterolateral myocardial infarction
30330	Acute q-wave infarct
41221	Acute septal infarction
12229	Acute st segment elevation myocardial infarction
3704	Acute subendocardial infarction
29758	Acute transmural myocardial infarction of unspecif site
14897	Anterior myocardial infarction nos
23708	Atrial septal defect/curr comp folow acut myocardal infarct
13566	Attack - heart
30421	Cardiac rupture following myocardial infarction (mi)
36423	Certain current complication follow acute myocardial infarct
2491	Coronary thrombosis
26975	Ecg: antero-septal infarct.
52705	Ecg: lateral infarction
59032	Ecg: myocardial infarct nos
7783	Ecg: myocardial infarction
55401	Ecg: subendocardial infarct
26972	Ecg:posterior/inferior infarct
50372	H/o: myocardial infarction in last year
24126	Haemopericardium/current comp folow acut myocard infarct
16408	Healed myocardial infarction
1204	Heart attack
1678	Inferior myocardial infarction nos
14898	Lateral myocardial infarction nos
1677	Mi - acute myocardial infarction
68357	Microinfarction of heart
4017	Old myocardial infarction
34803	Other acute myocardial infarction
46017	Other acute myocardial infarction nos
5387	Other specified anterior myocardial infarction
17464	Personal history of myocardial infarction
9555	Post infarct angina
23892	Posterior myocardial infarction nos
23579	Postmyocardial infarction syndrome
59189	Ruptur cardiac wall w'out haemopericard/cur comp fol ac mi
59940	Ruptur chordae tendinae/curr comp fol acute myocard infarct
49735	Rupture of papillary muscle

69474	Rupture papillary muscle/curr comp fol acute myocard infarct
17689	Silent myocardial infarction
18842	Subsequent myocardial infarction
45809	Subsequent myocardial infarction of anterior wall
38609	Subsequent myocardial infarction of inferior wall
72562	Subsequent myocardial infarction of other sites
46166	Subsequent myocardial infarction of unspecified site
13571	Thrombosis - coronary
29553	Thrombosis atrium,auric append&vent/curr comp foll acute mi
63467	True posterior myocardial infarction
37657	Ventric septal defect/curr comp fol acut myocardal infarctn
46276	Postoperative transmural myocardial infarction inferior wall
46112	Postoperative transmural myocardial infarction anterior wall
32272	Postoperative myocardial infarction
35119	Post infarction pericarditis
68748	Postoperative myocardial infarction, unspecified
41835	Postoperative subendocardial myocardial infarction
106812	Postoperative transmural myocardial infarction unspec site
39904	Ecg: old myocardial infarction
35674	H/o: myocardial infarct <60
40399	H/o: myocardial infarct >60

Congestive cardiac failure

Medcode	Description
21235	Suspected heart failure
9913	Heart failure confirmed
5155	O/e - pulmonary oedema
46672	New york heart assoc classification heart failure symptoms
18853	New york heart association classification - class i
13189	New york heart association classification - class ii
19066	New york heart association classification - class iii
51214	New york heart association classification - class iv
8464	Acute cor pulmonale
5141	Congestive cardiomyopathy
2062	Heart failure
1223	Cardiac failure
398	Congestive heart failure
2906	Congestive cardiac failure
10079	Right heart failure
10154	Right ventricular failure
9524	Biventricular failure
23707	Acute congestive heart failure
32671	Chronic congestive heart failure
27884	Decompensated cardiac failure
11424	Compensated cardiac failure
884	Left ventricular failure
43618	Pulmonary oedema - acute
5942	Impaired left ventricular function
5255	Acute left ventricular failure
27964	Acute heart failure
4024	Heart failure nos
17278	Cardiac failure nos
7321	Pulmonary oedema nos
558	Acute pulmonary oedema unspecified

48466	Acute oedema of lung, unspecified
5293	Acute pulmonary oedema nos
66306	Heart failure as a complication of care
26242	New york heart assoc classification heart failure symptoms
57987	Hyperten heart&renal dis+both(congestv)heart and renal fail
22262	Rheumatic left ventricular failure
20822	Congenital cardiac failure
72668	Malignant hypertensive heart disease with ccf
62718	Hypertensive heart disease nos with ccf
21837	Hypertensive heart&renal dis wth (congestive) heart failure

Other cardiac diseases

Medcode	Description
204	Hypertensive disease
351	High blood pressure
426	Sinus arrhythmia
561	Mitral regurgitation
562	Left ventricular hypertrophy
799	Essential hypertension
939	Endocarditis, valve unspecified, nos
999	Aortic stenosis, non-rheumatic
1005	Aortic regurgitation alone, cause unspecified
1007	Aortic incompetence alone, cause unspecified
1267	Mitral valve diseases
1268	Paroxysmal atrial fibrillation
1294	Mitral valve prolapse
1297	Paroxysmal atrial tachycardia
1344	Coronary artery disease
1381	Paroxysmal tachycardia nos
1414	Angina on effort
1430	Angina pectoris
1431	Unstable angina
1490	Heart disease nos
1535	Cardiac dysrhythmia nos
1536	Supraventricular tachycardia nos
1655	Triple vessel disease of the heart
1664	Atrial fibrillation
1757	Atrial flutter
1779	Tricuspid incompetence, non-rheumatic
1811	Other heart disease nos
1885	Mitral stenosis
1894	Benign essential hypertension
2155	Ventricular cardiac aneurysm
2212	Atrial fibrillation and flutter
2249	Ectopic beats unspecified
2343	Aortic stenosis alone, cause unspecified
2520	Pericardial effusion - acute

2579	Extrasystoles
2669	Pulmonary stenosis, cause unspecified
2724	Ventricular hypertrophy
2817	Tricuspid valve disorders, non-rheumatic
2977	Mitral valve incompetence
3032	Bundle branch block unspecified
3204	Cardiomyopathy
3399	Acute pericarditis
3418	Paroxysmal ventricular tachycardia
3499	Hypertrophic non-obstructive cardiomyopathy
3603	Partial atrioventricular block
3704	Acute subendocardial infarction
3712	Hypertension nos
3729	Ventricular dilatation
3757	Ecg: atrial fibrillation
3769	Stokes-adams syndrome
3810	Complete atrioventricular block
3849	Persistent sinus bradycardia
3909	Premature beats
3999	Single coronary vessel disease
4044	Cardiac dysrhythmias
4372	Systolic hypertension
4374	Ventricular fibrillation and flutter
4421	Heart beats irregular
4548	Aortic valve disorders
4549	Heart block
4656	Crescendo angina
4668	Hypertensive renal disease
4772	Skipped beat
4802	Ventricular ectopic beats
4827	Ventricular fibrillation
4915	Alcoholic cardiomyopathy
4939	Bacterial endocarditis
4940	Paroxysmal supraventricular tachycardia
5058	Mitral incompetence, non-rheumatic
5141	Congestive cardiomyopathy
5254	Double coronary vessel disease
5413	Coronary atherosclerosis
5449	Subacute bacterial endocarditis - sbe
5484	Ventricular flutter
5576	Sick sinus syndrome
5714	Atrioventricular dissociation
5743	Valvular heart disease
6077	Pulmonary regurgitation, cause unspecified
6331	Aneurysm of heart
6503	Cardiac arrhythmias
7005	Sinus tachycardia

7057	Hypertensive disease nos
7320	Ischaemic cardiomyopathy
7329	Secondary hypertension
7347	Unstable angina
7410	Sinoatrial node dysfunction nos
7457	Ectopic beats
7482	Left bundle branch hemiblock
7535	Primary dilated cardiomyopathy
7696	Syncope anginosa
7794	Ventricular tachycardia
7827	Other cardiac dysrhythmias
7839	Right ventricular thrombosis
7963	Aortic regurgitation - rheumatic
8010	Hypertrophic obstructive cardiomyopathy
8230	Wolff-parkinson-white syndrome
8274	Mitral and aortic stenosis
8411	Viral pericarditis nos
8568	Cardiac syndrome x
8651	Nodal rhythm disorder
8732	Bp - hypertensive disease
9023	Atrial premature depolarization
9276	Acute coronary insufficiency
9286	Tricuspid regurgitation, cause unspecified
9312	Chronic rheumatic heart disease
9391	Rheumatic aortic stenosis
9402	Secondary dilated cardiomyopathy
9413	Other acute and subacute ischaemic heart disease
9450	Mitral valve regurgitation
9479	Implant intravenous pacemaker for atrial fibrillation
9507	Acute non-q wave infarction
9515	Bigeminal pulse
9555	Post infarct angina
9563	Pulse missed beats
9591	Aortic stenosis
9906	Right bundle branch block
10078	Diseases of mitral and aortic valves
10109	Heart diseases
10111	Stenosis of unspecified heart valve
10187	Aortic regurgitation, non-rheumatic
10415	Myocarditis nos
10712	Trifascicular block
10818	Essential hypertension nos
10922	Mobitz type ii atrioventricular block
10964	Aortic valve stenosis with insufficiency
11048	Variant angina pectoris
11878	Mitral and aortic regurgitation
12149	First degree atrioventricular block

12312	Pulmonary valve disorders
12775	Acute and subacute endocarditis
12804	Stable angina
12986	Prinzmetal's angina
13250	Cardiac diseases
13854	Ecg: heart block
14646	Other and unspecified acute pericarditis
14723	Pulmonary stenosis, non-rheumatic
14998	Aortic incompetence, non-rheumatic
15089	Acute pericarditis in diseases ec nos
15106	Hypertensive renal disease nos
15132	Rheumatic endocarditis nos
15377	Malignant essential hypertension
15496	Pulmonary regurgitation, non-rheumatic
15534	Haemopericardium
15640	Pulmonary insufficiency, non-rheumatic
15643	Other specified chronic rheumatic heart disease
15661	Dressler's syndrome
15754	Other chronic ischaemic heart disease nos
15782	Chronic pulmonary heart disease nos
15792	Cardiac tamponade
15889	Atrial dilatation
15990	Endomyocardial fibrosis
16059	Secondary hypertension nos
16173	Hypertensive heart disease nos
16240	Postcardiotomy syndrome
16292	Hypertensive heart disease
16373	Tricuspid valve disease nec
16545	Rheumatic mitral valve disease
16996	Tb - acute pericarditis
17133	Mural thrombosis
17146	Other diseases of endocardium
17206	Bifascicular block
17307	Angina at rest
17434	Nephrosclerosis
17596	Mitral stenosis and aortic regurgitation
17597	Ecg: supraventricular arrhythmia
17840	Left bundle branch block
18100	Rheumatic aortic valve disease
18117	Other bundle branch block
18118	Worsening angina
18125	Nocturnal angina
18268	Severe sinus bradycardia
18293	Pericardial effusion - noninflammatory
18437	Sinoatrial block
18475	Combined disorders of mitral, aortic and tricuspid valves
18765	Other specified hypertensive disease

18877	Chronic pericarditis
18889	Asymptomatic coronary heart disease
19019	Aortic valve disorders nos
19191	Conduction disorders of heart
19337	Long q-t syndrome
19655	Angina at rest
19699	Disorders of both mitral and tricuspid valves
19707	Ecg: ventricular arrhythmia
19957	Pulmonary valve disorders nos
19979	Supraventricular ectopic beats
20001	Chronic rheumatic heart disease nos
20011	Hyperkinetic heart disease
20035	Thyrotoxic heart disease
20095	Angina decubitus
20157	Constrictive pericarditis
20416	Atherosclerotic heart disease
21807	Mitral incompetence - rheumatic
21837	Hypertensive heart&renal dis wth (congestive) heart failure
21844	Transient myocardial ischaemia
21852	Familial cardiomyopathy
21854	Left ventricular thrombosis
21980	Tricuspid regurgitation - rheumatic
22003	Regurgitation of unspecified heart valve
22262	Rheumatic left ventricular failure
22383	Other specified ischaemic heart disease
22412	Heart disease - pulmonary
22639	Acute myocarditis
22691	Romano - ward syndrome
22837	Mitral regurgitation - rheumatic
22993	Cardiomyopathy nos
23078	Chronic myocardial ischaemia
23437	Atrial fibrillation and flutter nos
23481	Asthma - cardiac
23494	Wandering atrial pacemaker
23608	Pulmonary incompetence, non-rheumatic
23619	Acute rheumatic pancarditis
23647	Paroxysmal atrioventricular tachycardia
23708	Atrial septal defect/curr comp folow acut myocardal infarct
24126	Haemopericardium/current comp folow acut myocard infarct
24377	Third degree atrioventricular block
24540	Chronic coronary insufficiency
24557	Mitral valve disorders nos
24636	Acute rheumatic pericarditis
24683	Myocardial degeneration
24783	Arteriosclerotic heart disease
25147	Anomalous atrioventricular excitation
25266	Paroxysmal tachycardia unspecified

25371	Secondary benign renovascular hypertension
25617	Acute and subacute bacterial endocarditis
25842	Angina pectoris nos
26318	Left main stem bundle branch block
26863	New onset angina
26973	Ecg:shows myocardial ischaemia
26975	Ecg: antero-septal infarct.
27375	Atrioventricular block nos
27413	Ectopic beats nos
27463	Pulsus alternans
27484	Cardiac aneurysm
27606	Acute pericarditis - unspecified
27683	Cardiomyopathy in myotonic dystrophy
27843	Infective endocarditis in diseases ec, nos
27874	Other conduction disorders
27928	Mobitz type i (wenckebach) atrioventricular block
27951	Other acute and subacute ischaemic heart disease
27977	Other acute and subacute ischaemic heart disease nos
28138	Other chronic ischaemic heart disease
28554	Angina pectoris nos
28662	Nonrheumatic mitral valve stenosis
28684	Hypertensive heart and renal disease with renal failure
28850	Heart valve disorders - non rheumatic
29158	Mitral and aortic valve disease nos
29180	Cardiac septal defect, acquired
29310	Renal hypertension
29371	Ecg: ventricular arrhythmia nos
29421	Silent myocardial ischaemia
29491	Paroxysmal nodal tachycardia
29551	Acute pericarditis in diseases ec
29654	Junctional premature depolarization
29902	Angina decubitus nos
30171	Other forms of heart disease
30443	Mitral valve disease nos
30454	Atrial thrombosis
30610	Aortic valve sclerosis
30667	Amyloid heart disease
31133	Other cardiac dysrhythmia nos
31286	Ecg: ventricular fibrillation
31308	Acute bacterial endocarditis
31341	Hypertension secondary to drug
31387	Secondary renovascular hypertension nos
31464	Hypertensive heart disease nos
31505	Rheumatic tricuspid stenosis
31690	Re-entry ventricular arrhythmia
31727	Mitral and aortic incompetence
31755	Secondary malignant hypertension

31759	Mitral incompetence and aortic stenosis
31784	Rupture of chordae tendinae
31809	Ventricular premature depolarization
31839	Mitral valve prolapse
31979	Endocarditis, valve unspecified
32059	Ventricular pre-excitation
32211	Rheumatic aortic insufficiency
32423	Hypertensive renal disease with renal failure
32435	Rheumatic mitral stenosis
32450	Ischaemic chest pain
33262	Mitral insufficiency and aortic stenosis
33348	Atrial hypertrophy
33370	Other pericardial disease nos
33673	Conduction disorders
33899	Cardiac arrest with successful resuscitation
33907	Mitral regurgitation and aortic stenosis
34065	Secondary pulmonary hypertension
34240	Mitral incompetence, cause unspecified
34290	Acute endocarditis nos
34326	Lown-ganong-levine syndrome
34328	Refractory angina
34437	Sarcoid myocarditis
34633	Other specified chronic ischaemic heart disease
34744	Hypertension secondary to endocrine disorders
34869	Tricuspid incompetence, cause unspecified
34932	Pulmonary valve stenosis with insufficiency
35119	Post infarction pericarditis
35124	Paroxysmal supraventricular tachycardia nos
35127	Non-rheumatic atrial fibrillation
35372	Tricuspid regurgitation, non-rheumatic
35713	Other specified chronic ischaemic heart disease nos
35724	Tricuspid stenosis, non-rheumatic
35947	Right fascicular block
36193	Other specified heart disease
36227	Conduction disorders nos
36423	Certain current complication follow acute myocardial infarct
36496	Acute pericarditis - pneumococcal
36609	Atherosclerotic cardiovascular disease
36629	Second degree atrioventricular block
36755	Acute pericarditis nos
36768	Rheumatic pulmonary valve disease nos
36854	Coronary artery spasm
36886	Acute rheumatic endocarditis
37628	Calcification of pericardium
37657	Ventric septal defect/curr comp fol acut myocardal infarctn
38299	Pulmonary insufficiency, cause unspecified
38817	Non-traumatic pneumopericardium

38876	Acute and subacute endocarditis unspecified
39003	Other bundle branch block nos
39423	Diphtheritic myocarditis
39449	Coronary thrombosis not resulting in myocardial infarction
39546	[x]other forms of angina pectoris
39649	Malignant hypertensive renal disease
39671	Incompetence of unspecified heart valve
39693	Subendocardial ischaemia
39843	Other heart block
39916	Mitral valve leaf prolapse
39956	Jervell and lange-nielsen syndrome
40239	Multiple valve diseases
40427	Other diseases of pericardium
40569	Chronic bacterial endocarditis
40582	Disorders of both aortic and tricuspid valves
40793	Papillary muscle degeneration
40834	Other primary cardiomyopathy nos
40949	Mitral valve insufficiency
40956	Acute pericarditis - uraemic
40957	Adherent rheumatic pericardium
41163	Pericardial 'milk spots'
41179	Other ill-defined heart disease nos
41221	Acute septal infarction
41488	Constrictive cardiomyopathy
41527	Acute myocarditis nos
41677	Aneurysm of heart nos
41916	Ventricular fibrillation and flutter nos
42014	Cardiac dilatation nos
42024	Other specified pericardial disease nos
42043	Secondary cardiomyopathy nos
42128	Tricuspid insufficiency, cause unspecified
42229	Secondary hypertension nos
42239	Tricuspid incompetence - rheumatic
42803	Anomalous atrioventricular excitation nos
42901	Kyphoscoliotic heart disease
43347	Aortic incompetence - rheumatic
43816	Rheumatoid carditis
43855	Tricuspid valve disorders nos
43935	Benign hypertensive renal disease
43937	Papillary muscle atrophy
44096	Conduction disorders unspecified
44167	Rheumatic pulmonary valve disease
44328	Mitral stenosis with regurgitation
44376	Chronic rheumatic pericarditis
44488	Mitral stenosis with insufficiency
44756	Rheumatic fever with heart involvement
45174	Acute and subacute bacterial endocarditis nos

45311	Pericardial effusion - acute
46178	Other heart block nos
46237	Endocarditis in disease ec
46294	Chronic pulmonary heart disease
46736	Pulmonary incompetence, cause unspecified
46992	Prolonged p-r interval
47037	Sarcoid heart disease
47637	[x]other forms of chronic ischaemic heart disease
47887	Aortic insufficiency, non-rheumatic
48024	Subacute endocarditis nos
48099	Acute rheumatic myocarditis
48340	Acute and subacute infective endocarditis in diseases ec
49185	Aortic valve calcification
49272	[x]other aortic valve disorders
49355	Mitral stenosis and aortic insufficiency
49551	Tricuspid stenosis and regurgitation, cause unspecified
49735	Rupture of papillary muscle
49787	Rheumatoid myocarditis
49844	Beriberi heart disease
50157	Malignant hypertensive heart disease
50720	Adhesive pericarditis
50788	Accelerated atrioventricular conduction
50809	Rheumatic aortic valve disease nos
50983	Mitral stenosis with incompetence
51140	Electromechanical dissociation with successful resuscitation
51472	Endocarditis, valve unspecified, os
51635	Secondary benign hypertension nos
51845	Paroxysmal junctional tachycardia
51879	Rheumatic mitral insufficiency
52127	Benign hypertensive heart disease with ccf
52271	Nonrheumatic tricuspid valve stenosis with insufficiency
52427	Benign hypertensive heart disease
52517	[x]ischaemic heart diseases
53518	Acute myocarditis - coxsackie
53756	[x]other mitral valve diseases
53826	Left bundle branch hemiblock nos
53878	Rheumatic heart disease unspecified
53893	[x]other specified cardiac arrhythmias
53959	[x]other pulmonary valve disorders
54088	Rheumatic pulmonary insufficiency
54113	Other chronic pulmonary heart disease
54478	Endocardial fibroelastosis
54535	Stenocardia
54554	Interventricular block nos
55416	Toxic myocarditis
55646	Acute myocarditis - influenzal
55850	Cardiomyopathy in disease ec

56029	Tricuspid stenosis, cause unspecified
56180	Concato's disease
56621	Cardiovascular arteriosclerosis unspecified
57069	Right bbb with left anterior fascicular block
57126	Acute pericarditis - tuberculous
57288	Secondary benign hypertension
57306	Other primary cardiomyopathies
57334	Gouty tophi of heart
57338	Multiple valve disease, unspecified
57633	Ruptured mitral valve cusp
57916	Other diseases of pericardium os
57980	Other and unspecified rheumatic heart disease
57987	Hyperten heart&renal dis+both(congestv)heart and renal fail
58032	Atrioventricular block unspecified
58769	Acute pericarditis - coxsackie
58810	Aortic insufficiency alone, cause unspecified
58938	Cardiomyopathy due to drugs and other external agents
59102	Acute idiopathic pericarditis
59140	Pick's disease of heart
59189	Ruptur cardiac wall w'out haemopericard/cur comp fol ac mi
59193	Aneurysm of coronary vessels
59213	Fatty infiltration heart
59275	Rheumatic valvulitis, chronic nos
59383	Secondary malignant renovascular hypertension
59677	Acute pericarditis - streptococcal
59687	Other ill-defined heart disease
59854	Other rheumatic heart disease nos
60047	Essential paroxysmal tachycardia
60266	Rheumatic tricuspid insufficiency
60411	Pyopericardium
61072	Myocardial infarction aborted
61124	Cardiac hypertrophy nos
61166	Hypertensive heart disease nos without ccf
61250	Mitral stenosis and aortic incompetence
61379	Acute pericarditis - meningococcal
61492	Acute myocarditis, unspecified
61660	Benign hypertensive heart disease without ccf
61774	Papillary muscle scarring
61878	Pulmonary stenosis, cause unspecified
61929	Fistula of pericardium
62186	Rheumatic tricuspid stenosis and incompetence
62207	Rheumatic pulmonary stenosis
62349	Left anterior fascicular block
62404	Rheumatic myocarditis
62494	Endocarditis - typhoid
62626	Acute papillary muscle infarction
62718	Hypertensive heart disease nos with ccf

62736	Acute myocarditis in diseases ec, nos
63000	Benign hypertensive heart and renal disease
63078	Other acute myocarditis nos
63217	Acute pulmonary heart disease
63466	Hypertensive heart and renal disease
63675	Fibrosis of pericardium
63960	Rheumatic aortic stenosis with insufficiency
64481	Acute purulent pericarditis unspecified
64673	Nutritional and metabolic cardiomyopathy nos
64837	Dystrophic cardiomyopathy
65073	Other conduction disorders nos
65533	Acute pulmonary heart disease nos
65653	Right fascicular block
65807	Constrictive pericarditis nos
66121	Acute and subacute endocarditis unspecified, nos
66388	Status anginosus
67087	Other cardiac wall aneurysm
67232	Malignant hypertensive heart and renal disease
67291	Acute myocarditis - toxoplasmosis
67528	Papillary muscle disease
67780	Endocarditis - q fever
68126	Other chronic rheumatic endocardial disease
68401	[x]other forms of acute ischaemic heart disease
68411	Acute myocarditis - meningococcal
68659	Hypertensive heart and renal disease nos
68685	Obscure african cardiomyopathy
68766	Congestive obstructive cardiomyopathy
68849	Acute rheumatic heart disease nos
68979	[x]other forms of heart disease
69216	Accessory atrioventricular conduction
69474	Rupture papillary muscle/curr comp fol acute myocard infarct
69593	Endocarditis - coxsackie
69753	[x]hypertensive diseases
69809	Left posterior fascicular block
69995	Rheumatic chorea with heart involvement
70366	Bouveret-hoffmann syndrome
70648	[x]other hypertrophic cardiomyopathy
70698	Multiple mitral and aortic valve involvement
70855	Cardiomyopathy in friedreich's ataxia
71004	[x]aortic valve disorders in diseases classified elsewhere
71046	Other chronic pulmonary heart disease nos
71848	Septic myocarditis nos
72110	Other acute myocarditis
72306	Tricuspid stenosis and insufficiency, cause unspecified
72409	Idiopathic myocarditis nos
72562	Subsequent myocardial infarction of other sites
72613	Rheumatic tricuspid valve disease nos

72628	Chronic rheumatic myopericarditis
72653	Other bilateral bundle branch block
72888	Pre-excitation atrioventricular conduction
73153	[x]myocarditis in viral diseases classified elsewhere
73283	Becker's disease
73293	Secondary malignant hypertension nos
73540	Other acute rheumatic heart disease
83473	Diastolic hypertension
89579	Insufficiency of unspecified heart valve
91774	Acquired atrioventricular fistula of heart
91847	Acute myocarditis - tuberculous
92266	[x]other restrictive cardiomyopathy
92267	Papillary muscle dysfunction
93113	Rheumatic tricuspid stenosis and regurgitation
93114	Rheumatic tricuspid stenosis and insufficiency
94521	[x]other rheumatic aortic valve diseases
94870	Congestive heart failure due to valvular disease
94872	Mitral and aortic insufficiency
95334	Malignant hypertensive heart disease without ccf
95488	[x]pulmon heart disease & diseases of pulmonary circulation
95919	Brugada syndrome
96076	Persistent atrial fibrillation
96101	Adhesive pericarditis nos
96277	Permanent atrial fibrillation
96799	Post cardiac operation heart failure nos
96838	[x]acute transmural myocardial infarction of unspecif site
97160	[x]other specified conduction disorders
97533	[x]hypertension secondary to other renal disorders
97617	[x]other cardiomyopathies
97738	Tricuspid insufficiency, non-rheumatic
97780	Arrhythmogenic right ventricular cardiomyopathy
97821	[x]other and unspecified right bundle-branch block
98020	Cardiomyopathy in diseases ec, nos
98167	Giant cell myocarditis
98538	Nonrheumatic tricuspid valve disorder, unspecified
98560	[x]other nonrheumatic mitral valve disorders
98634	[x]cardiomyopathy in metabolic diseases ce
98638	[x]other acute myocarditis
98675	Right bbb with left posterior fascicular block
98751	Right ventricular dilatation
99051	[x]cardiovascular disease, unspecified
99077	[x]other tricuspid valve diseases
99338	External ventricular defibrillation
99959	Post cardiac operation functional disturbance
100051	[x]other acute rheumatic heart disease
100572	Endocarditis - gonococcal
100907	[x]other forms of acute pericarditis

100910	[x]multiple valve disorders/diseases ce
100924	Acute myoendocarditis nos
100966	Nutritional and metabolic cardiomyopathies
101015	Takotsubo cardiomyopathy
101485	Pacemaker twiddler's syndrome
101712	[x]other specified heart block
101922	[x]other and unspecified fascicular block
102458	[x]other secondary hypertension
102955	Tachycardiomyopathy
103046	Malignant hypertensive heart disease nos
103752	Mobitz type 1 second degree atrioventricular block
103850	Acute pericarditis - gonococcal
104081	Acute pericarditis - staphylococcal
104373	Septic myocarditis - pneumococcal
104529	Tachycardia-induced cardiomyopathy
104658	Stress cardiomyopathy
104697	Acute aseptic myocarditis of the newborn
104876	Right ventricular diastolic dysfunction
105192	Pericardial effusion
105226	Suspected arrhythmia
105250	Mural cardiac aneurysm
105274	Stage 2 hypertension (nice - nat ins for hth clin excl 2011)
105316	Stage 1 hypertension
105371	Stage 1 hypertension (nice - nat ins for hth clin excl 2011)
105479	Coronary microvascular disease
105480	Hypertension resistant to drug therapy
105487	Severe hypertension
105615	Other acute rheumatic heart disease nos
105626	Rheumatic pulmonary stenosis and insufficiency
105651	Amyloid cardiomyopathy
105798	Cardiac amyloidosis
105938	Benign hypertensive heart disease nos
105989	Severe hypertension (nat inst for health clinical ex 2011)
106049	[x]other and unspecified atrioventricular block
106928	[x]other diseases of pulmonary vessels
107257	Septic myocarditis - staphylococcal
107462	Rheumatic heart disease
107472	Paroxysmal atrial flutter
107591	Carditis due to rheumatic fever
107662	Chronic pericardial effusion
107704	Primary hypertension
107770	Papillary muscle disorder nos
108136	Stage 1 hyperten (nice 2011) without evidnce end organ damge
108180	Right ventricular systolic dysfunction
108258	[x]pericarditis in other diseases classified elsewhere
109797	Stage 1 hyperten (nice 2011) with evidnce end organ damge
109821	Atrial standstill

110488	[x]tricuspid valve disorders/diseases ce
110531	[x]endocarditis,valve unspecified,in diseases ce
110634	[x]other specified pulmonary heart diseases
110717	[x]acute myocarditis, unspecified
111837	Acute myocarditis in diseases ec
112041	Acute pericarditis - syphilitic
112042	Acute myocarditis - syphilitic
112442	[x]pericarditis in bacterial diseases classified elsewhere

Cerebrovascular disease

Medcode	Description
73901	[x]cerebrovascular diseases
96630	[x]intracerebral haemorrhage in hemisphere; unspecified
92036	[x]occlusion and stenosis of other cerebral arteries
90572	[x]occlusion and stenosis of other precerebral arteries
53810	[x]other intracerebral haemorrhage
19280	Anterior cerebral artery syndrome
8443	Brain stem stroke syndrome
13564	Cerebellar haemorrhage
17322	Cerebellar stroke syndrome
54744	Cerebral degeneration due to cerebrovascular disease
27975	Cerebral infarction due to embolism of cerebral arteries
1298	Cva unspecified
7017	Evacuation of intracerebral haematoma nec
34135	H/o: cva/stroke
5871	H/o: stroke
5051	Intracerebral haemorrhage
31060	Intracerebral haemorrhage in hemisphere; unspecified
3535	Intracerebral haemorrhage nos
30202	Intracerebral haemorrhage; intraventricular
57315	Intracerebral haemorrhage; multiple localized
20284	Intracranial haemorrhage nos
7780	Left sided cva
28314	Left sided intracerebral haemorrhage; unspecified
18689	Middle cerebral artery syndrome
98642	Multiple and bilateral precerebral arterial occlusion
71274	Occlusion??? Of multiple and bilat cerebral arteries
51326	Other precerebral artery occlusion
19354	Other transient cerebral ischaemia
19260	Posterior cerebral artery syndrome
45781	Precerebral arterial occlusion
71585	Precerebral artery occlusion nos
33499	Pure motor lacunar syndrome
51767	Pure sensory lacunar syndrome
12833	Right sided cva
19201	Right sided intracerebral haemorrhage; unspecified
29939	Ruptured berry aneurysm
48149	Sequelae of intracerebral haemorrhage
63830	Stenosis of precerebral arteries
6155	Stroke due to cerebral arterial occlusion
18604	Stroke due to intracerebral haemorrhage

6253	Stroke unspecified
18912	Subdural haemorrhage nos
504	Transient cerebral ischaemia
15788	Transient cerebral ischaemia nos
1895	Transient cerebral ischaemia nos
8181	Traumatic subdural haemorrhage
111096	[x]other specified cerebrovascular diseases
65745	[x]other subarachnoid haemorrhage
108668	[x]subarachnoid haemorrhage from other intracranial arteries
2418	Cerebrovascular disease
10062	Cerebrovascular disease nos
38304	Closed traumatic subarachnoid haemorrhage
6960	Cva - cerebrovascular accid due to intracerebral haemorrhage
6116	Cva - cerebrovascular accident unspecified
40053	Generalised ischaemic cerebrovascular disease nos
12555	Generalised ischaemic cerebrovascular disease nos
23361	Late effects of cerebrovascular disease
96717	Open traumatic subarachnoid haemorrhage
13577	Other cerebrovascular disease
37493	Other cerebrovascular disease nos
34117	Other cerebrovascular disease os
51311	Other specified cerebrovascular disease
44740	Sequelae of subarachnoid haemorrhage
51138	Sequelae/other unspecified cerebrovascular diseases
1469	Stroke and cerebrovascular accident unspecified
17326	Subarachnoid haemorrh from intracranial artery; unspecif
1786	Subarachnoid haemorrhage
28807	Subarachnoid haemorrhage following injury
42331	Subarachnoid haemorrhage from anterior communicating artery
41910	Subarachnoid haemorrhage from basilar artery
56007	Subarachnoid haemorrhage from carotid siphon and bifurcation
19412	Subarachnoid haemorrhage from middle cerebral artery
9696	Subarachnoid haemorrhage from posterior communicating artery
60692	Subarachnoid haemorrhage from vertebral artery
23580	Subarachnoid haemorrhage nos
58545	Traumatic subarachnoid haemorrhage
99367	[x]other cerebrovascular disorders in diseases ce
108630	[x]subarachnoid haemorrh from intracranial artery, unspecif
70536	Acute cerebrovascular insufficiency nos
569	Infarction - cerebral
63360	Subarachnoid haemorrhage due to birth injury
106511	Subarachnoid h'ge inj + open intracran wnd+concussion unspec
102130	Subarachnoid h'ge inj no open intracran wnd+no loss consc
10792	Stroke monitoring
16956	Cerebral palsy; not congenital or infantile; acute
45002	Perinatal subarachnoid haemorrhage

Diabetes without complications

Medcode	Description
52212	[X]Diabetes mellitus
41686	[X]Other specified diabetes mellitus
112365	[X]Pre-existing diabetes mellitus, unspecified
7059	Admit diabetic emergency

711	Diabetes mellitus
43453	Diabetes mellitus autosomal dominant
36695	Diabetes mellitus autosomal dominant type 2
61122	Diabetes mellitus induced by non-steroid drugs
11551	Diabetes mellitus induced by steroids
72345	Diabetes mellitus NOS with hyperosmolar coma
42505	Diabetes mellitus NOS with ketoacidosis
65062	Diabetes mellitus NOS with ketoacidotic coma
50972	Diabetes mellitus NOS with no mention of complication
70821	Diabetes mellitus NOS with other specified manifestation
65025	Diabetes mellitus NOS with peripheral circulatory disorder
21482	Diabetes mellitus with hyperosmolar coma
1682	Diabetes mellitus with ketoacidosis
15690	Diabetes mellitus with ketoacidotic coma
38986	Diabetes mellitus with no mention of complication
33343	Diabetes mellitus with other specified manifestation
110997	Diabetes mellitus, juvenile, + other specified manifestation
14803	Diabetes mellitus; adult onset; no mention of complication
43139	Diabetes mellitus; adult onset; with hyperosmolar coma
54856	Diabetes mellitus; adult onset; with ketoacidosis
63371	Diabetes mellitus; adult; other specified manifestation
24490	Diabetes mellitus; juvenile type; no mention of complication
40023	Diabetes mellitus; juvenile type; with hyperosmolar coma
53200	Diabetes mellitus; juvenile type; with ketoacidosis
42567	Diabetes mellitus; juvenile type; with ketoacidotic coma
12675	Diabetes: shared care programme
43951	Diabetic - cooperative patient
13071	Diabetic - good control
2378	Diabetic - poor control
22023	Diabetic - poor control NOS
6125	Diabetic annual review
8842	Diabetic on insulin
28769	Diabetic on insulin and oral treatment
1684	Diabetic on oral treatment
34152	Diabetic peripheral angiopathy
24363	Diabetic stabilisation
36633	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
18505	IDDM-Insulin dependent diabetes mellitus
31310	Insulin dependent diabetes maturity onset
97849	Insulin dependent diabetes maturity onset
1038	Insulin dependent diabetes mellitus
1647	Insulin dependent diabetes mellitus
51261	Insulin dependent diabetes mellitus
6791	Insulin dependent diabetes mellitus - poor control
72702	Insulin dependent diabetes mellitus - poor control
44440	Insulin dependent diabetes mellitus with hypoglycaemic coma
37648	Insulin treated non-insulin dependent diabetes mellitus
1407	Insulin treated Type 2 diabetes mellitus
18278	Insulin treated Type 2 diabetes mellitus
18264	Insulin treated Type II diabetes mellitus
64668	Insulin treated Type II diabetes mellitus
56448	Insulin-dependent diabetes without complication
99719	Insulin-dependent diabetes without complication
43857	Lipoatrophic diabetes mellitus
52236	Malnutrition-related diabetes mellitus
66675	Malnutrition-related diabetes mellitus with coma

33969	Malnutrition-related diabetes mellitus with ketoacidosis
14889	Maturity onset diabetes
46624	Maturity onset diabetes in youth
98392	Maturity onset diabetes in youth type 1
59991	Maturity onset diabetes in youth type 2
5884	NIDDM - Non-insulin dependent diabetes mellitus
8403	Non-insulin dependant diabetes mellitus - poor control
506	Non-insulin dependent diabetes mellitus
43785	Non-insulin dependent diabetes mellitus with hypoglyca coma
4513	Non-insulin-dependent diabetes mellitus
29979	Non-insulin-dependent diabetes mellitus without complication
59288	Other specified diabetes mellitus with coma
38617	Other specified diabetes mellitus with ketoacidosis
12213	Patient on maximal tolerated therapy for diabetes
50960	Pre-existing diabetes mellitus; insulin-dependent
50609	Pre-existing diabetes mellitus; non-insulin-dependent
55431	Pre-existing diabetes mellitus; unspecified
109133	Pre-existing malnutrition-related diabetes mellitus
22487	Secondary diabetes mellitus
94383	Secondary diabetes mellitus without complication
51697	Secondary pancreatic diabetes mellitus
96506	Secondary pancreatic diabetes mellitus without complication
32193	Steroid induced diabetes
26108	Steroid induced diabetes mellitus without complication
1549	Type 1 diabetes mellitus
17858	Type 1 diabetes mellitus
35288	Type 1 diabetes mellitus - poor control
45914	Type 1 diabetes mellitus - poor control
40682	Type 1 diabetes mellitus maturity onset
97446	Type 1 diabetes mellitus maturity onset
39070	Type 1 diabetes mellitus with hypoglycaemic coma
70766	Type 1 diabetes mellitus with hypoglycaemic coma
10692	Type 1 diabetes mellitus with ketoacidosis
40837	Type 1 diabetes mellitus with ketoacidotic coma
69676	Type 1 diabetes mellitus without complication
111106	Type 1 diabetes mellitus without complication
758	Type 2 diabetes mellitus
17859	Type 2 diabetes mellitus
25627	Type 2 diabetes mellitus - poor control
45913	Type 2 diabetes mellitus - poor control
46917	Type 2 diabetes mellitus with hypoglycaemic coma
61071	Type 2 diabetes mellitus with hypoglycaemic coma
32627	Type 2 diabetes mellitus with ketoacidosis
51756	Type 2 diabetes mellitus with ketoacidotic coma
47954	Type 2 diabetes mellitus without complication
105784	Type 2 diabetes mellitus without complication
12455	Type I diabetes mellitus
24423	Type I diabetes mellitus
46850	Type I diabetes mellitus - poor control
105337	Type I diabetes mellitus - poor control
63017	Type I diabetes mellitus maturity onset
96235	Type I diabetes mellitus maturity onset
42729	Type I diabetes mellitus with hypoglycaemic coma
62209	Type I diabetes mellitus with ketoacidosis
66145	Type I diabetes mellitus with ketoacidotic coma
62613	Type I diabetes mellitus without complication

95992	Type I diabetes mellitus without complication
18219	Type II diabetes mellitus
22884	Type II diabetes mellitus
24458	Type II diabetes mellitus - poor control
47315	Type II diabetes mellitus - poor control
56268	Type II diabetes mellitus with hypoglycaemic coma
53392	Type II diabetes mellitus without complication
109103	Type II diabetes mellitus without complication
9013	Unstable diabetes
26855	Unstable insulin dependent diabetes mellitus
54600	Unstable insulin dependent diabetes mellitus
43921	Unstable type 1 diabetes mellitus
97474	Unstable type 1 diabetes mellitus
49949	Unstable type I diabetes mellitus
60107	Unstable type I diabetes mellitus

Diabetes with complications

Medcode	Description
99628	[X]Glomerular disorders in diabetes mellitus
100292	[X]Unspecified diabetes mellitus with renal complications
10099	Advanced diabetic maculopathy
35107	Diabetes mellitis with nephropathy NOS
22573	Diabetes mellitus NOS with neurological manifestation
34283	Diabetes mellitus NOS with ophthalmic manifestation
16230	Diabetes mellitus with neurological manifestation
7795	Diabetes mellitus with neuropathy
33254	Diabetes mellitus with ophthalmic manifestation
16491	Diabetes mellitus with polyneuropathy
68843	Diabetes mellitus, adult onset, with ketoacidotic coma
35105	Diabetes mellitus, adult onset, with renal manifestation
68792	Diabetes mellitus, juvenile type, + unspecified complication
67853	Diabetes mellitus, juvenile, + neurological manifestation
39317	Diabetes mellitus; adult onset; neurological manifestation
41389	Diabetes mellitus; adult onset; ophthalmic manifestation
69748	Diabetes mellitus; juvenile type; ophthalmic manifestation
93922	Diabetes mellitus; juvenile type; with renal manifestation
32556	Diabetes with gangrene
2340	Diabetic amyotrophy
59903	Diabetic amyotrophy
10659	Diabetic cataract
3837	Diabetic maculopathy
37315	Diabetic mononeuropathy
2475	Diabetic nephropathy
2342	Diabetic neuropathy
5002	Diabetic polyneuropathy
1323	Diabetic retinopathy
11626	Diabetic retinopathy NOS
18056	Foot abnormality - diabetes related
65463	High risk non proliferative diabetic retinopathy
30477	High risk proliferative diabetic retinopathy
34450	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
39809	Insulin dependent diab mell with neuropathic arthropathy
44260	Insulin dependent diabetes mellitus with diabetic cataract

100770	Insulin dependent diabetes mellitus with diabetic cataract
109051	Insulin dependent diabetes mellitus with gangrene
99716	Insulin dependent diabetes mellitus with hypoglycaemic coma
24694	Insulin dependent diabetes mellitus with mononeuropathy
45276	Insulin dependent diabetes mellitus with multiple complicat
52104	Insulin dependent diabetes mellitus with multiple complicatn
57621	Insulin dependent diabetes mellitus with nephropathy
102163	Insulin dependent diabetes mellitus with nephropathy
41716	Insulin dependent diabetes mellitus with polyneuropathy
101311	Insulin dependent diabetes mellitus with polyneuropathy
6509	Insulin dependent diabetes mellitus with retinopathy
93875	Insulin dependent diabetes mellitus with retinopathy
98704	Insulin dependent diabetes mellitus with ulcer
52283	Insulin-dependent diabetes mellitus with neurological comps
101735	Insulin-dependent diabetes mellitus with neurological comps
49276	Insulin-dependent diabetes mellitus with ophthalmic comps
98071	Insulin-dependent diabetes mellitus with ophthalmic comps
46963	Insulin-dependent diabetes mellitus with renal complications
102946	Insulin-dependent diabetes mellitus with renal complications
45499	Kimmelstiel - Wilson disease
100347	Malnutritn-relat diabetes melitus wth periph circul complctn
39420	Myasthenic syndrome due to diabetic amyotrophy
10755	Non proliferative diabetic retinopathy
69278	Non-insulin depend diabetes mellitus with diabetic cataract
40962	Non-insulin dependent d m with neuropathic arthropathy
72320	Non-insulin dependent diabetes mellitus with mononeuropathy
59365	Non-insulin dependent diabetes mellitus with nephropathy
45467	Non-insulin dependent diabetes mellitus with polyneuropathy
54212	Non-insulin-dependent d m with peripheral angiopath
55842	Non-insulin-dependent diabetes mellitus with neuro comps
50429	Non-insulin-dependent diabetes mellitus with ophthalm comps
52303	Non-insulin-dependent diabetes mellitus with renal comps
17262	Non-insulin-dependent diabetes mellitus with retinopathy
47144	O/E - diabetic maculopathy absent both eyes
9835	O/E - diabetic maculopathy present both eyes
49640	O/E - left chronic diabetic foot ulcer
35116	O/E - Left diabetic foot - ulcerated
11129	O/E - left eye background diabetic retinopathy
13108	O/E - left eye diabetic maculopathy
13103	O/E - left eye preproliferative diabetic retinopathy
13101	O/E - left eye proliferative diabetic retinopathy
52041	O/E - left eye stable treated prolif diabetic retinopathy
62384	O/E - right chronic diabetic foot ulcer
35316	O/E - Right diabetic foot - ulcerated
17095	O/E - Right diabetic foot at risk
11433	O/E - right eye background diabetic retinopathy
13102	O/E - right eye diabetic maculopathy
13099	O/E - right eye preproliferative diabetic retinopathy
13097	O/E - right eye proliferative diabetic retinopathy
47328	O/E - right eye stable treated prolif diabetic retinopathy
52630	O/E - sight threatening diabetic retinopathy
46290	Other specified diabetes mellitus with multiple comps
61523	Other specified diabetes mellitus with neurological comps
47377	Other specified diabetes mellitus with ophthalmic complicatn
112402	Other specified diabetes mellitus with periph circ comps
13279	Other specified diabetes mellitus with renal complications

11599	Pan retinal photocoagulation for diabetes
63555	Polyneuropathy in disease NOS
2986	Preproliferative diabetic retinopathy
3286	Proliferative diabetic retinopathy
22967	Retinal abnormality - diabetes related
49554	Type 1 diabetes mellitus with diabetic cataract
110400	Type 1 diabetes mellitus with diabetic cataract
22871	Type 1 diabetes mellitus with exudative maculopathy
55239	Type 1 diabetes mellitus with gastroparesis
68105	Type 1 diabetes mellitus with mononeuropathy
47650	Type 1 diabetes mellitus with multiple complications
10418	Type 1 diabetes mellitus with nephropathy
42831	Type 1 diabetes mellitus with neurological complications
61829	Type 1 diabetes mellitus with neurological complications
18230	Type 1 diabetes mellitus with neuropathic arthropathy
54008	Type 1 diabetes mellitus with neuropathic arthropathy
47649	Type 1 diabetes mellitus with ophthalmic complications
102740	Type 1 diabetes mellitus with ophthalmic complications
30294	Type 1 diabetes mellitus with persistent microalbuminuria
46301	Type 1 diabetes mellitus with polyneuropathy
21983	Type 1 diabetes mellitus with renal complications
47582	Type 1 diabetes mellitus with renal complications
18387	Type 1 diabetes mellitus with retinopathy
41049	Type 1 diabetes mellitus with retinopathy
68390	Type 1 diabetes mellitus with ulcer
44779	Type 2 diabetes mellitus with diabetic cataract
44982	Type 2 diabetes mellitus with diabetic cataract
25591	Type 2 diabetes mellitus with exudative maculopathy
46150	Type 2 diabetes mellitus with gangrene
63690	Type 2 diabetes mellitus with gastroparesis
62674	Type 2 diabetes mellitus with mononeuropathy
65267	Type 2 diabetes mellitus with multiple complications
108005	Type 2 diabetes mellitus with multiple complications
12640	Type 2 diabetes mellitus with nephropathy
24836	Type 2 diabetes mellitus with nephropathy
34268	Type 2 diabetes mellitus with neurological complications
45919	Type 2 diabetes mellitus with neurological complications
35385	Type 2 diabetes mellitus with neuropathic arthropathy
66965	Type 2 diabetes mellitus with neuropathic arthropathy
47321	Type 2 diabetes mellitus with ophthalmic complications
70316	Type 2 diabetes mellitus with ophthalmic complications
18425	Type 2 diabetes mellitus with polyneuropathy
109865	Type 2 diabetes mellitus with polyneuropathy
18209	Type 2 diabetes mellitus with renal complications
18777	Type 2 diabetes mellitus with renal complications
18496	Type 2 diabetes mellitus with retinopathy
42762	Type 2 diabetes mellitus with retinopathy
17545	Type I diabetes mellitus with diabetic cataract
97894	Type I diabetes mellitus with exudative maculopathy
102112	Type I diabetes mellitus with gangrene
99231	Type I diabetes mellitus with mononeuropathy
91942	Type I diabetes mellitus with multiple complications
108007	Type I diabetes mellitus with multiple complications
66872	Type I diabetes mellitus with nephropathy
49146	Type I diabetes mellitus with neurological complications
60208	Type I diabetes mellitus with neuropathic arthropathy

99311	Type I diabetes mellitus with ophthalmic complications
102620	Type I diabetes mellitus with persistent microalbuminuria
91943	Type I diabetes mellitus with polyneuropathy
61344	Type I diabetes mellitus with renal complications
109837	Type I diabetes mellitus with renal complications
38161	Type I diabetes mellitus with retinopathy
95343	Type I diabetes mellitus with retinopathy
93878	Type I diabetes mellitus with ulcer
48192	Type II diabetes mellitus with diabetic cataract
93727	Type II diabetes mellitus with diabetic cataract
111798	Type II diabetes mellitus with exudative maculopathy
104323	Type II diabetes mellitus with gangrene
98723	Type II diabetes mellitus with hypoglycaemic coma
106528	Type II diabetes mellitus with ketoacidosis
106061	Type II diabetes mellitus with ketoacidotic coma
50813	Type II diabetes mellitus with mononeuropathy
95351	Type II diabetes mellitus with mononeuropathy
43227	Type II diabetes mellitus with multiple complications
64571	Type II diabetes mellitus with nephropathy
102201	Type II diabetes mellitus with nephropathy
67905	Type II diabetes mellitus with neurological complications
98616	Type II diabetes mellitus with neurological complications
47816	Type II diabetes mellitus with neuropathic arthropathy
109197	Type II diabetes mellitus with neuropathic arthropathy
59725	Type II diabetes mellitus with ophthalmic complications
100964	Type II diabetes mellitus with ophthalmic complications
104639	Type II diabetes mellitus with peripheral angiopathy
85991	Type II diabetes mellitus with persistent microalbuminuria
60796	Type II diabetes mellitus with persistent proteinuria
47409	Type II diabetes mellitus with polyneuropathy
50527	Type II diabetes mellitus with polyneuropathy
50225	Type II diabetes mellitus with renal complications
57278	Type II diabetes mellitus with renal complications
49655	Type II diabetes mellitus with retinopathy
58604	Type II diabetes mellitus with retinopathy
91646	Type II diabetes mellitus with ulcer
64449	Unspecified diabetes mellitus with multiple complications
18642	Type 1 diabetes mellitus with arthropathy
62352	Type I diabetes mellitus with arthropathy
65616	Insulin dependent diabetes mellitus with arthropathy
103902	Type II diabetes mellitus with arthropathy
49869	Type 2 diabetes mellitus with arthropathy
59253	Type 2 diabetes mellitus with arthropathy
24693	Non-insulin dependent diabetes mellitus with arthropathy
18143	Type II diabetes mellitus with arthropathy

Peptic ulcer disease

Medcode	Description
68661	Acute peptic ulcer without mention of complication
32856	Acute peptic ulcer
15175	Duodenal ulcer nos
64710	Resection of gastric ulcer by cautery
63718	Endoscopic injection haemostasis of gastric ulcer

23688	Operations on gastric ulcer
23087	Perforated chronic duodenal ulcer
18625	Bleeding chronic duodenal ulcer
55933	Operation on duodenal ulcer nos
24021	Peptic ulcer of oesophagus
44335	Acute duodenal ulcer without mention of complication
18027	Acute duodenal ulcer
24040	Acute gastric ulcer
57958	Unspecified gastric ulcer with haemorrhage
14671	Acute gastric ulcer with perforation
63001	Anti-platelet induced gastric ulcer
67356	Chronic gastric ulcer with obstruction
53336	Chronic gastric ulcer with perforation
50497	Unspecified peptic ulcer
67082	Unspecified peptic ulcer without mention of complication
64111	Unspecified peptic ulcer with perforation
45184	Acute gastrojejunal ulcer
102177	Acute gastrojejunal ulcer with perforation
110244	Chronic gastrojejunal ulcer with haemorrhage and perforation
63482	Unspecified gastrojejunal ulcer
40489	[v]personal history of duodenal ulcer
6321	H/o: duodenal ulcer
51406	Chronic duodenal ulcer nos
4741	Closure of perforated duodenal ulcer
6865	Stomach ulcer operations
94104	Other specified operation on gastric ulcer
29317	Recurrent duodenal ulcer
44324	Acute gastric ulcer nos
4643	Peptic ulcer symptoms
52138	Chronic duodenal ulcer unspecified
33438	Chronic duodenal ulcer without mention of complication
71881	Chronic duodenal ulcer with haemorrhage and perforation
18654	Chronic gastric ulcer
36461	Unspecified gastric ulcer with perforation
48946	Chronic gastric ulcer without mention of complication
44309	Chronic gastric ulcer nos
66092	Unspecified gastrojejunal ulcer nos
53669	Unspecified duodenal ulcer
67711	Acute peptic ulcer unspecified
41271	[v] personal history of gastric ulcer
60346	Unspecified gastrojejunal ulcer with haemorrhage
73338	Unspecified gastric ulcer without mention of complication
352	Duodenal ulcer - (du)
71403	Acute gastric ulcer with haemorrhage and perforation
22918	Duodenal ulcer disease
44284	Unspecified gastric ulcer nos
64556	Chronic gastric ulcer unspecified
70390	Chronic peptic ulcer unspecified
109546	Acute gastric ulcer with obstruction
94397	Unspec gastric ulcer; unspec haemorrhage and/or perforation
99430	Chronic peptic ulcer without mention of complication
9981	Jejunal ulcer
96090	Chronic gastrojejunal ulcer
44073	Chronic duodenal ulcer with obstruction
3462	Duodenal erosion
15403	Gastrojejunal ulcer nos

37643	Chronic duodenal ulcer with perforation
96628	Acute gastrojejunal ulcer with haemorrhage
69663	Chronic peptic ulcer nos
11104	Perforated chronic gastric ulcer
9853	Chronic duodenal ulcer
73697	Unspecified gastric ulcer with obstruction
2812	H/o: peptic ulcer
45278	Primary ulcer of intestine
5928	Operations on duodenal ulcer
657	Unspecified duodenal ulcer with perforation
3101	Pyloric ulcer
64014	Closure of gastric ulcer nec
53747	Ulceration of intestine nos
53797	Acute duodenal ulcer nos
30054	Acute gastric ulcer with haemorrhage
33914	Operation on gastric ulcer nos
2814	Unspecified duodenal ulcer with haemorrhage
50048	Acute peptic ulcer nos
20677	Closure of perforated gastric ulcer
56005	Other specified operation on duodenal ulcer
18319	Healed gastric ulcer leaving a scar
26261	[v]personal history of peptic ulcer
71904	Unspecified duodenal ulcer with obstruction
60249	Unspecified peptic ulcer nos
18324	Acute duodenal ulcer with perforation
24342	Acute gastric ulcer unspecified
11124	Bleeding acute gastric ulcer
99670	Unspecified peptic ulcer with obstruction
89227	Anti-platelet induced gastric ulcer nos
37620	Chronic peptic ulcer with perforation
85989	Non steroidal anti inflammatory drug induced duodenal ulcer
19928	Peptic ulcer nos
52323	Multiple gastric ulcers
7108	H/o: gastric ulcer
71897	Chronic gastric ulcer with haemorrhage and perforation
36583	Bleeding chronic gastric ulcer
70456	Unspecified peptic ulcer with haemorrhage
92695	Balfour excision of gastric ulcer
53081	Unspecified gastric ulcer
84227	Repair perforated gastric ulcer
48730	Acute duodenal ulcer with haemorrhage and perforation
64913	Gastrocolic ulcer
70005	Suture of ulcer of stomach nec
40997	Chronic peptic ulcer
73417	Acute duodenal ulcer with obstruction
89234	Anti-platelet induced duodenal ulcer
55350	Oversew of blood vessel of duodenal ulcer
23082	Gastrojejunal ulcer (gju)
96622	Unspecified peptic ulcer with haemorrhage and perforation
71150	Unspecified duodenal ulcer without mention of complication
15821	Stress ulcer nos
5521	Acute peptic ulcer with perforation
52313	Chronic peptic ulcer with obstruction
63582	Chronic gastric ulcer with haemorrhage
53822	Acute duodenal ulcer unspecified
42274	Acute gastrojejunal ulcer nos

65737	Unspecified duodenal ulcer nos
670	Peptic ulcer - (pu) site unspecified
15979	Unspecified gastrojejunal ulcer with perforation
37268	Suture of duodenal ulcer not elsewhere classified
1262	Gastric ulcer - (gu)
45981	Endoscopic injection haemostasis of duodenal ulcer
28366	Unspec duodenal ulcer; unspec haemorrhage and/or perforation
18001	Acute duodenal ulcer with haemorrhage
89023	Non steroidal anti inflammatory drug induced gastric ulcer
90899	Repair perforated peptic ulcer
106330	Acute gastrojejunal ulcer with haemorrhage and perforation
48951	Chronic duodenal ulcer with haemorrhage
93436	Unspecified duodenal ulcer with haemorrhage and perforation
45304	Acute peptic ulcer with haemorrhage and perforation
64165	Acute gastric ulcer without mention of complication
53126	Chronic peptic ulcer with haemorrhage
29771	Gastric ulcer nos
44637	Acute peptic ulcer with haemorrhage
6333	Prepyloric ulcer

Connective tissue disease

Medcode	Description
45284	Systemic lupus erythematosus with renal
57313	Polyneuropathy in collagen vascular disease
47465	Polyneuropathy in polyarteritis nodosa
71258	Polyneuropathy in collagen vascular disease NOS
6599	Muscular dystrophies and other myopathies
63541	Symptomatic inflammatory myopathy in disease EC
57888	Myopathy due to polyarteritis nodosa
43816	Rheumatoid carditis
62323	Polyarteritis nodosa and allied conditions
1471	Polyarteritis nodosa
68136	Polyarteritis nodosa and allied conditions NOS
58750	Nephrotic syndrome in polyarteritis nodosa
79981	Sero negative rheumatoid arthritis
77143	Sero positive rheumatoid arthritis
10953	Arthropathies and related disorders
31438	Diffuse diseases of connective tissue
57675	Libman-Sacks disease
36942	Drug-induced systemic lupus erythematosus
68277	Acrosclerosis
110174	Systemic sclerosis induced by drugs and chemicals
23552	Felty's syndrome
56838	Caplan's syndrome
10919	Sero negative polyarthritis
96456	Endemic polyarthritis
1408	Polymyalgia rheumatica
29472	Giant cell arteritis with polymyalgia rheumatica
93927	Polymyositis ossificans
43192	Scoliosis in connective tissue anomalies
16640	Musculoskeletal or connective tissue diseases OS
43085	[X]Addtnl musculskeletal+connectv tissue dis classfctn terms
52860	[X]Systemic connective tissue disorders

68965	[X]Other systemic diseases of connective tissue
92421	[X]Systemic disorders/connective tissue in other diseases CE
25642	[X]Other disord musculoskeletal system and connective tissue
28247	Unspecified anomaly of connective tissue
44095	Polyneuropathy in disseminated lupus erythematosus
62401	Polyneuropathy in rheumatoid arthritis
108072	Myopathy due to disseminated lupus erythematosus
31209	Myopathy due to rheumatoid arthritis
55601	Myopathy due to scleroderma
94751	Eyelid discoid lupus erythematosus
9954	Rheumatoid lung
94996	Lung disease with systemic sclerosis
42940	Lung disease with polymyositis
31564	Lung disease with systemic lupus erythematosus
47672	Nephrotic syndrome in systemic lupus erythematosus
22205	Lupus nephritis
4125	Lupus erythematosus
33449	Lupus erythematosus chronicus
2667	Discoid lupus erythematosus
40797	Lupus erythematosus migrans
65391	Lupus erythematosus nodularis
46148	Lupus erythematosus profundus
44984	Lupus erythematosus tumidus
63955	Lupus erythematosus unguium mutilans
25390	Subacute cutaneous lupus erythematosus
7522	Lupus erythematosus NOS
100692	[X]Other local lupus erythematosus
10885	Musculoskeletal and connective tissue diseases
22509	Collagen diseases
7871	Systemic lupus erythematosus
20007	Disseminated lupus erythematosus
29519	Systemic lupus erythematosus with organ or sys involv
11920	Systemic lupus erythematosus with pericarditis
42719	Systemic lupus erythematosus NOS
3670	Scleroderma
28417	Systemic sclerosis
44141	Progressive systemic sclerosis
15511	Polymyositis
20271	Other specified diffuse collagen diseases
21151	Collagen disease NOS
27603	Rheumatoid arthritis and other inflammatory polyarthropathy
844	Rheumatoid arthritis
21358	Rheumatoid arthritis of shoulder
107963	Rheumatoid arthritis of sternoclavicular joint
100914	Rheumatoid arthritis of acromioclavicular joint
59738	Rheumatoid arthritis of elbow
63365	Rheumatoid arthritis of distal radio-ulnar joint
48832	Rheumatoid arthritis of wrist
42299	Rheumatoid arthritis of MCP joint
41941	Rheumatoid arthritis of PIP joint of finger
63198	Rheumatoid arthritis of DIP joint of finger
49067	Rheumatoid arthritis of hip
100776	Rheumatoid arthritis of sacro-iliac joint
50863	Rheumatoid arthritis of knee
107791	Rheumatoid arthritis of tibio-fibular joint
51239	Rheumatoid arthritis of ankle

73619	Rheumatoid arthritis of subtalar joint
70658	Rheumatoid arthritis of talonavicular joint
71784	Rheumatoid arthritis of other tarsal joint
51238	Rheumatoid arthritis of 1st MTP joint
99414	Rheumatoid arthritis of lesser MTP joint
107112	Rheumatoid arthritis of IP joint of toe
6916	Seronegative rheumatoid arthritis
8350	Flare of rheumatoid arthritis
46436	Rheumatoid lung disease
9707	Seropositive errosive rheumatoid arthritis
12019	Seropositive rheumatoid arthritis; unspecified
31724	Rheumatoid lung
28853	Fibrosing alveolitis associated with rheumatoid arthritis
106440	[X]Rheumatoid arthritis
93715	[X]Other seropositive rheumatoid arthritis
70221	[X]Other specified rheumatoid arthritis
56202	[X]Seropositive rheumatoid arthritis; unspecified
58706	[X]Other forms of systemic lupus erythematosus
71763	[X]Other forms of systemic sclerosis
2175	Musculoskeletal and connective tissue diseases NOS
6639	H/O: rheumatoid arthritis
33264	O/E-hands-rheumatoid spindling
24641	Circumscribed scleroderma
73485	Unspecified circumscribed scleroderma
25463	Linear scleroderma
72288	Circumscribed scleroderma NOS
4909	Connective tissue diseases
99435	Neonatal lupus erythematosus
17675	CREST syndrome
4908	Dermatomyositis
40387	Poikilodermatomyositis
32649	Juvenile dermatomyositis
91559	Dermatopolymyositis in neoplastic disease
28316	Dermatopolymyositis, unspecified
44743	Rheumatoid arthritis of cervical spine
44203	Other rheumatoid arthritis of spine
30548	Rheumatoid vasculitis
18155	Rheumatoid bursitis
53621	Rheumatoid nodule
31054	Rheumatoid arthritis - multiple joint
49227	Other rheumatoid arthropathy + visceral/systemic involvement
8583	Rheumatic carditis
5723	Rheumatoid nodule
37431	Rheumatoid arthropathy + visceral/systemic involvement NOS
4186	Juvenile rheumatoid arthritis - Still's disease
50644	Juvenile rheumatoid arthropathy unspecified
47831	Acute polyarticular juvenile rheumatoid arthritis
21533	Pauciarticular juvenile rheumatoid arthritis
36276	Monarticular juvenile rheumatoid arthritis
27557	Juvenile rheumatoid arthritis NOS
3944	Chronic post-rheumatic arthropathy
58543	Nodular fibrositis of chronic rheumatic disease
31360	Juvenile rheumatoid arthritis
53862	[X]Other dermatomyositis
95437	[X]Dermatopolymyositis, unspecified
83529	[X]Mixed connective tissue disease

9614	Rheumatism, excluding the back
33474	Rheumatism and fibrositis unspecified
1029	Rheumatism unspecified
17085	Muscular rheumatism
35937	Rheumatism or fibrositis NOS
35759	Other specified nonarticular rheumatism
15205	Nonarticular rheumatism NOS

Peripheral vascular disease

Medcode	Description
14796	[D]Failure of peripheral circulation
4970	[D]Gangrene
37750	[D]Gangrene NOS
53634	[D]Gangrene of toe in diabetic
51634	[D]Gangrene; spreading cutaneous
30484	[D]Peripheral circulatory failure
31053	[D]Widespread diabetic foot gangrene
18423	Arterial insufficiency
23497	Buerger's disease
6853	Claudication
108675	Congenital anomaly of peripheral vascular system OS
61062	Congenital peripheral aneurysm
65025	Diabetes mellitus NOS with peripheral circulatory disorder
35399	Diabetes mellitus with peripheral circulatory disorder
63357	Diabetes mellitus, adult, + peripheral circulatory disorder
70448	Diabetes mellitus, juvenile +peripheral circulatory disorder
32556	Diabetes with gangrene
12735	Gangrene of foot
5414	Gangrene of toe
69124	IDDM with peripheral circulatory disorder
1826	Ischaemia of legs
56803	NIDDM with peripheral circulatory disorder
54212	Non-insulin-dependent d m with peripheral angiopath
11680	O/E - gangrene
9454	Other aneurysm
73738	Other congenital anomaly of peripheral vascular system NOS
45384	Other peripheral vascular system anomalies
41728	Other specified pulmonary circulation disease NOS
18269	Peripheral arterio-venous aneurysm
9204	Peripheral gangrene
6827	Peripheral ischaemia
5702	Peripheral ischaemic vascular disease
16148	Peripheral vascular complications of care
44528	Peripheral vascular complications of care NOS
56429	Peripheral vascular system anomaly NOS
40068	Presenile gangrene
102719	[X]Aortic aneurysm of unspecified site; nonruptured
102725	[X]Aortic aneurysm of unspecified site; ruptured
73961	[X]Other specified peripheral vascular diseases
17345	AAA - Abdominal aortic aneurysm without mention of rupture
17767	Abdominal aortic aneurysm which has ruptured
1867	Abdominal aortic aneurysm without mention of rupture
1735	Aortic aneurysm

6872	Aortic aneurysm NOS
1736	Aortic aneurysm repair
16034	Aortic aneurysm without mention of rupture NOS
34152	Diabetic peripheral angiopathy
16521	Dissecting aortic aneurysm
17220	Emergency repair of aortic aneurysm
16993	H/O: aortic aneurysm
59534	H/O: Peripheral vascular disease procedure
28109	Inflammatory abdominal aortic aneurysm
64446	Insulin dependent diab mell with peripheral angiopathy
1517	Intermittent claudication
45521	Juxtarenal aortic aneurysm
9759	Leaking abdominal aortic aneurysm
5943	Other peripheral vascular disease
38907	Other specified peripheral vascular disease
4325	Other specified peripheral vascular disease NOS
2760	Peripheral vascular disease NOS
3530	Peripheral vascular disease NOS
13572	Ruptured abdominal aortic aneurysm
15304	Ruptured aortic aneurysm NOS
63920	Ruptured suprarenal aortic aneurysm
16800	Ruptured thoracic aortic aneurysm
27563	Thoracic aortic aneurysm which has ruptured
23532	Thoracic aortic aneurysm without mention of rupture
11430	Thoracoabdominal aortic aneurysm; ruptured
40787	Thoracoabdominal aortic aneurysm; without mention of rupture
63408	Tube graft abdominal Aortic aneurysm (emergency)
26232	Tube graft of Abdominal aortic aneurysm
93468	Type 1 diabetes mellitus with peripheral angiopathy
60699	Type 2 diabetes mellitus with peripheral angiopathy
37806	Type 2 diabetes mellitus with peripheral angiopathy
54899	Type II diabetes mellitus with peripheral angiopathy
104639	Type II diabetes mellitus with peripheral angiopathy
51166	Y graft abdominal Aortic aneurysm
92925	Y graft of abdominal Aortic aneurysm (emergency)
70260	Aortic aneurysm - syphilitic
103613	Aortic aneurysm monitoring
91462	Endov insertion of stent graft for thoracic aortic aneurysm
83577	Endovas ins stent graft for infrarenal abdom aortic aneurysm
94682	Endovas insert of stent graft for suprarenal aortic aneurysm
99859	Endovas insert stent for aortic aneurysm of bifurcation nec
97217	Endovascul insert stent infrarenal abdominal aortic aneurysm
98542	Endovascular insertion of stent for thoracic aortic aneurysm
106780	Endovascular insertion stent for suprarenal aortic aneurysm
100195	Endovascular stenting for aortic aneurysm of bifurcation nec
70446	Endovascular stenting infrarenal abdominal aortic aneurysm
97030	Endovascular stenting of suprarenal aortic aneurysm
51061	Endovascular stenting of thoracic aortic aneurysm
101379	Infrarenal abdominal aortic aneurysm
18499	Peripheral vascular disease monitoring
106260	Peripheral vascular disease monitoring first letter
106224	Peripheral vascular disease monitoring invitation
106660	Peripheral vascular disease monitoring second letter
106855	Peripheral vascular disease monitoring third letter
62061	Syphilitic aortic aneurysm

Cognitive impairment, including dementia

Medcode	Description
1993	Memory loss - amnesia
3639	Amnesia symptom
5777	Memory loss symptom
2908	Memory disturbance
27788	Temporary loss of memory
103453	Short-term memory loss
39507	Poor visual sequential memory
40821	Poor auditory sequential memory
67163	Disturbance of memory for order of events
110307	Memory impairment
7674	Cognitive decline
107282	Mild cognitive impairment
107482	Moderate cognitive impairment
107402	Severe cognitive impairment
108266	Cognitive impairment
52947	Memory: own age not known
53146	Memory: present time not known
53014	Memory: present place not known
52948	Memory: present year not known
53125	Memory: own dob not known
52825	Memory: present month not known
52800	Memory: important event not known
52801	Memory: important person not known
52805	Memory: count down unsuccessful
53016	Memory: address recall unsuccessful
65856	Gds level 2 - very mild cognitive decline
60263	Gds level 3 - mild cognitive decline
60726	Gds level 4 - moderate cognitive decline
70057	Gds level 5 - moderately severe cognitive decline
94717	Gds level 6 - severe cognitive decline
72520	Gds level 7 - very severe cognitive decline
6387	Mild memory disturbance
6061	Organic memory impairment
11936	[x]mild cognitive disorder
110729	[x]cognitive communication disorder
31572	Visual disorientation syndrome
7711	[d]memory deficit
20683	[d]disorientation, unspecified
112378	[x]symptoms/signs involving cognition, percept, emotion state & behaviour
52939	[x]other & unspecified symptom/signs involving cognitive function/awareness
52811	[x]disorientation, unspecified
10822	Impaired cognition
61639	Unable to recognise surroundings
47279	Mistakes people's identity
67565	Does not recognise self
61869	Does not recognise photographs of self
92635	Unable to recognise parts of own body
101458	Unable to recognise objects
100788	Unable to recognise faces
91516	Unable to recognise familiar people
59539	Unable to reason
52550	Difficulty reasoning
46554	Unable to use verbal reasoning

46320	Difficulty using verbal reasoning
99474	Difficulty using visuospatial reasoning
48506	Unable to process information
50446	Difficulty processing information
61308	Unable to process information accurately
57609	Difficulty processing information accurately
109311	Unable to process information at normal speed
99588	Difficulty processing information at normal speed
56044	Unable to analyse information
57608	Difficulty analysing information
50843	Difficulty performing logical sequencing
66172	Isolated memory skills
19719	Orientation confused
64219	Orientation poor
66012	Disorientation for person
55460	Spatial disorientation
51379	Memory disturbance (& amnesia (& symptom))
67838	Memory loss symptom
103375	Memory loss - amnesia
105538	Memory disturbance
102880	Loss of memory
10123	Memory loss
68230	Memory gone
12805	Memory loss - amnesia
19297	Loss of memory
12277	Lom - loss of memory
32367	Impairment of working memory
65696	Impairment of primary memory
37191	Poor memory for remote events
9786	Loss of memory for recent events
67802	No memory for recent events
67998	Temporary loss of memory
47882	Transient memory loss
10514	Memory impairment
39915	Memory dysfunction
50418	Memory deficit
26434	Bad memory
12057	Memory problem
12583	Poor memory
19073	Memory lapses
51739	Distortion of memory
64892	Invents experiences to compensate for loss of memory
11410	Poor short-term memory
10571	Short-term memory loss
53978	Poor long-term memory
47581	Long-term memory loss
98798	Delayed verbal memory
46860	Difficulty making plans
46564	Difficulty making decisions
53388	Unable to use decision-making strategies
107021	Difficulty using decision-making strategies
65319	Unable to make considered choices
43204	Difficulty making considered choices
59242	Difficulty solving problems
40002	Language-related cognitive disorder
1916	Senile dementia

1350	Senile/presenile dementia
7323	Uncomplicated senile dementia
15165	Presenile dementia
42602	Uncomplicated presenile dementia
30032	Presenile dementia with paranoia
27677	Presenile dementia with depression
38438	Presenile dementia nos
44674	Senile dementia with depressive or paranoid features
18386	Senile dementia with paranoia
21887	Senile dementia with depression
41089	Senile dementia with depressive or paranoid features nos
37015	Senile dementia with delirium
19477	Arteriosclerotic dementia
43089	Uncomplicated arteriosclerotic dementia
55467	Arteriosclerotic dementia with paranoia
43292	Arteriosclerotic dementia with depression
42279	Arteriosclerotic dementia nos
25386	Dementia in conditions ec
4951	Chronic confusional state
7664	[x]dementia in alzheimer's disease
49263	[x]dementia in alzheimer's disease with early onset
25704	[x]presenile dementia,alzheimer's type
60059	[x]primary degen dementia, alzheimer's type, presenile onset
61528	[x]alzheimer's disease type 2
38678	[x]dementia in alzheimer's disease with late onset
46762	[x]alzheimer's disease type 1
11379	[x]senile dementia,alzheimer's type
43346	[x]primary degen dementia of alzheimer's type, senile onset
30706	[x]dementia in alzheimer's dis, atypical or mixed type
29386	[x]dementia in alzheimer's disease, unspecified
8195	[x]alzheimer's dementia unspec
6578	[x]vascular dementia
9565	[x]arteriosclerotic dementia
46488	[x]vascular dementia of acute onset
55838	[x]predominantly cortical dementia
8934	[x]subcortical vascular dementia
31016	[x]mixed cortical and subcortical vascular dementia
55313	[x]other vascular dementia
19393	[x]vascular dementia, unspecified
12621	[x]dementia in other diseases classified elsewhere
28402	[x]dementia in pick's disease
26270	[x]lewy body dementia
64267	[x]dementia in other specified diseases classif elsewhere
4693	[x] unspecified dementia
48501	[x] presenile dementia nos
34944	[x] primary degenerative dementia nos
4357	[x] senile dementia nos
27759	[x] senile dementia, depressed or paranoid type
1917	Alzheimer's disease
16797	Alzheimer's disease with early onset
32057	Alzheimer's disease with late onset
11136	Pick's disease
29512	Senile degeneration of brain
7572	Lewy body disease
59122	[x]other alzheimer's disease
8634	Multi infarct dementia

11175	[x]multi-infarct dementia
9509	[x]dementia in parkinson's disease
49513	Presenile dementia with delirium
53446	[x]delirium superimposed on dementia
56912	Arteriosclerotic dementia with delirium

Mild liver disease

Medcode	Description
107896	[x]chronic viral hepatitis, unspecified
108343	[x]other chronic viral hepatitis
21713	Alcoholic fibrosis and sclerosis of liver
7957	Autoimmune chronic active hepatitis
9029	Chronic active hepatitis
1755	Chronic aggressive hepatitis
7602	Chronic alcoholic hepatitis
66534	Chronic lobular hepatitis
23578	Chronic persistent hepatitis
26367	Chronic viral hepatitis
24813	Chronic viral hepatitis b with delta-agent
41096	Chronic viral hepatitis b without delta-agent
30586	Chronic viral hepatitis c
32277	Chronic viral hepatitis, unspecified
42843	Other non-alcoholic chronic liver disease
39351	Toxic liver disease with chronic active hepatitis
64750	Toxic liver disease with chronic lobular hepatitis
17219	Toxic liver disease with chronic persistent hepatitis
6015	[x]other and unspecified cirrhosis of liver
4743	Alcoholic cirrhosis of liver
73482	Bacterial portal cirrhosis
9494	Biliary cirrhosis
58630	Biliary cirrhosis nos
91591	Biliary cirrhosis of children
40567	Capsular portal cirrhosis
1754	Chronic hepatitis
15489	Chronic hepatitis nos
53877	Chronic hepatitis unspecified
16725	Cirrhosis - non alcoholic
6863	Cirrhosis and chronic liver disease
1638	Cirrhosis of liver nos
18739	Cryptogenic cirrhosis of liver
3450	Diffuse nodular cirrhosis
44676	Fatty portal cirrhosis
68376	Florid cirrhosis
19512	Glycogenosis with hepatic cirrhosis
92909	Hypertrophic portal cirrhosis
48928	Infectious cirrhosis nos
96664	Juvenile portal cirrhosis
100474	Laennec's cirrhosis
22841	Macronodular cirrhosis of liver
69204	Multilobular portal cirrhosis
16455	Non-alcoholic cirrhosis nos
8206	Pigmentary cirrhosis of liver
47257	Portal cirrhosis

55454	Portal cirrhosis unspecified
5638	Primary biliary cirrhosis
15424	Secondary biliary cirrhosis
112044	Syphilitic portal cirrhosis
44120	Toxic liver disease with fibrosis and cirrhosis of liver
100253	Xanthomatous portal cirrhosis
109540	Zooparasitic portal cirrhosis
111969	Chronic hepatitis annual review
99898	Chronic hepatitis annual review - enhanced services admin
102922	Cystic fibrosis related cirrhosis
10539	Chronic liver disease nos
33597	Other non-alcoholic chronic liver disease nos

Severe liver disease

Medcode	Description
105611	[X]Oesophageal varices in diseases classified elsewhere
48102	Other sequelae of chronic liver disease
73139	Oesophageal varices without bleeding in diseases EC
5129	Portal hypertension
24989	Oesophageal varices with bleeding
30655	Oesophageal varices without bleeding
47214	Rigid oesophagoscopic injection sclerotherapy oesoph varices
1641	Oesophageal varices
62582	Oesophageal varices in diseases EC NOS
10636	Hepatorenal syndrome
10797	Oesophageal varices NOS
108800	Liver abscess and chronic liver disease causing sequelae NOS
23511	Hepatic coma
96756	Oesophageal varices with bleeding in diseases EC
26319	Oesophageal varices in cirrhosis of the liver
44424	Oesophageal varices in diseases EC
89587	Other specified viral hepatitis with hepatic coma NOS
8363	Oesophageal varices in alcoholic cirrhosis of the liver
89445	Auxillary liver transplant
65050	Viral hepatitis C with coma
69053	Viral hepatitis B with coma
99745	O/E - breath musty - hepatic
47861	Exploration of liver transplant
99250	Other specified transplantation of liver
55962	Viral hepatitis A with coma
71422	Heterotopic transplantation of liver
112028	[X]Unspecified viral hepatitis with coma
64451	Central haemorrhagic necrosis of liver
100073	Piggy back liver transplant
69552	Other specified viral hepatitis with coma
32025	Orthotopic transplantation of liver
69194	Replacement of previous liver transplant
4405	Transplantation of liver
111975	Unspecified viral hepatitis with coma
22411	Encephalopathy - hepatic
89717	fibreopt endoscop rubber band ligation of upper git varices
16759	fibreoptic endoscopic banding of oesophageal varices
11960	fibreoptic endoscopic injection sclerotherapy oesoph varices

43404	local ligation of oesophageal varices
20912	open injection sclerotherapy to oesophageal varices
20233	open operation on oesophageal varices nos
24220	open operations on oesophageal varices
107975	other specified open operation on oesophageal varices
46647	rigid oesophagoscopic banding of oesophageal varices
62038	tanner devascularisation for bleeding varices
11972	varices - other
111976	viral hepatitis with hepatic coma
31897	liver abscess and sequelae of chronic liver disease

Hemiplegia

Medcode	Description
20122	Spastic hemiplegia
1749	Hemiplegia
3063	Paraplegia
8492	Hemiplegia nos
8933	Left hemiplegia
3293	Right hemiplegia
22135	O/e - hemiplegia
46175	Flaccid paraplegia
39085	Flaccid hemiplegia
9375	Spastic paraplegia
3514	Hereditary spastic paraplegia
36133	O/e - paraplegia
58576	Tropical spastic paraplegia
59494	Massive muscular calcification associated with paraplegia
37160	Congenital paraplegia
27966	Congenital hemiplegia
2019	Infantile hemiplegia nos
99040	Paraplegia - congenital

Cancers

Medcode	Description
17177	H/o: * leukaemia
19692	Suspected leukaemia
2755	Cancers
111289	Malignant neoplasm of upper lip; buccal aspect
112660	Malignant neoplasm of lip unspecified; frenulum
112528	Malignant neoplasm of vestibule of mouth nos
110775	Malignant neoplasm of interlobular biliary canals
108667	Angiosarcoma of spleen
110993	Malignant neoplasm of first metacarpal bone
108638	Malignant neoplasm of third metacarpal bone
111779	Malignant neoplasm of patella
111426	Malignant neoplasm of second metatarsal bone
110192	Malig neopl of connective and soft tissue - sacrum or coccyx
111311	Malignant neoplasm; overlap lesion connective & soft tissue
109002	Malignant melanoma of perianal skin
112379	Malignant neoplasm of extraocular muscle of orbit
110766	Malignant neoplasm of cerebral dura mater

109473	Malignant neoplasm of cerebral pia mater
108886	Hodgkin's mixed cellularity of lymph nodes inguinal and leg
111942	Hodgkin's lymphocytic depletion of head; face and neck
110563	Hodgkin's lymphocytic depletion lymph nodes inguinal and leg
111766	Nodular lymphoma of lymph nodes of axilla and upper limb
112570	Malignant histiocytosis of lymph nodes of axilla and arm
110903	Malignant histiocytosis of lymph nodes of multiple sites
109342	Unspec malig neop lymphoid/histiocytic of intrapelvic nodes
37182	Multiple myeloma and immunoproliferative neoplasms
112440	Other myeloid leukaemia
108715	Histiocytic leukaemia
63653	Heilmeyer - schoner disease
20564	[m]carcinoma in situ nos
21914	[m]intraepithelial carcinoma nos
1950	[m]transitional cell papillomas and carcinomas
27827	[m]adenocarcinoma in situ
111172	[m]carcinoid tumour, argentaffin, malignant
42273	[m]papillary adenomas and adenocarcinomas
40632	[m]mucinous adenoma and adenocarcinoma
112307	[m]interstitial cell tumour, malignant
17366	[m]soft tissue tumours and sarcomas nos
100371	Epithelial nephroblastoma
112383	Pancreatoblastoma
104147	[m]infantile embryonal carcinoma
22712	[m]epithelioid haemangioendothelioma nos
108682	[m]germinoblastic sarcoma nos
43459	Plasma cell tumours
64068	Plasma cell tumour nos
110349	[m]plasma cell leukaemia nos
111904	[x]malignant neoplasm/upper resp tract; part unspecified
109714	[x]oth and unspecif peripheral & cutaneous t-cell lymphomas
51718	Histiocytosis x , chronic
36736	Histiocytosis x , unspecified
37126	Histiocytosis, unspecified
40000	Langerhans' cell histiocytosis
111040	Langerhans' cell histiocytosis
36020	[x]other histiocytosis syndromes
12106	[v]personal history of malignant neoplasm
62814	[v]personal history of malig neop of gastrointestinal tract
68018	[v]personal history of malignant neoplasm of anus
64568	[v]personal history of malig neop of gastrointestinal tract
57727	[v]personal history of malignant neoplasm of large intestine
58177	[v]personal history of malignant neoplasm of liver
51001	[v]personal history of malignant neoplasm of oesophagus
62785	[v]personal history of malignant neoplasm of rectum
49447	[v]personal history of malignant neoplasm of stomach
99931	[v]personal history of malignant neoplasm of tongue
49289	[v]personal history of malig neop of trachea/bronchus/lung
32246	[v]personal history of malignant neoplasm of bronchus
29284	[v]personal history of malignant neoplasm of lung
72262	[v]personal history of malig neop other intrathoracic organ
61655	[v]personal history of malignant neoplasm - accessory sinus
43311	[v]personal history of malignant neoplasm of larynx
39863	[v]personal history of malignant neoplasm of nose
16639	[v]personal history of malignant neoplasm of breast
9444	[v]personal history of malignant neoplasm of genital organ

23936	[v]personal history of malignant neoplasm of cervix uteri
109429	[v]personal history of malignant neoplasm of genital organ
52141	[v]personal history of malignant neoplasm of ovary
37306	[v]personal history of malignant neoplasm of prostate
48808	[v]personal history of malignant neoplasm of testis
46779	[v]personal history of malignant neoplasm of uterine body
30322	[v]personal history of malignant neoplasm of urinary organ
35816	[v]personal history of malignant neoplasm of bladder
47683	[v]personal history of malignant neoplasm of kidney
28881	[v]personal history of malignant neoplasm of kidney
36693	[v]personal history of leukaemia
94597	[v]personal history of lymphoid leukaemia
110058	[v]personal history of myeloid leukaemia
72204	[v]personal history other lymphatic/haematopoietic neoplasm
40561	[v]personal history of hodgkin's disease
66457	[v]personal history of other specified malignant neoplasm
46282	[v]personal history of malignant neoplasm of bone
48085	[v]personal history of malignant neoplasm of brain
103100	[v]personal history of malignant neoplasm of eye
47669	[v]personal history of malignant neoplasm of skin
35771	[v]personal history of malignant neoplasm of thyroid
45803	[v]personal history of malignant neoplasm of tongue
68612	[v]personal history of unspecified malignant neoplasm
60918	Lymphoma stage i
94935	Lymphoma stage ii
32240	Lymphoma stage iii
71672	Lymphoma stage iv
44617	Hiv disease resulting in burkitt's lymphoma
66367	Hiv dis resulting oth types of non-hodgkin's lymphoma
69767	[x]hiv disease resulting in other non-hodgkin's lymphoma
19415	Malignant neoplasm of lip; oral cavity and pharynx
24374	Carcinoma of lip; oral cavity and pharynx
14712	Malignant neoplasm of lip
9984	Carcinoma of lip
73962	Malignant neoplasm of upper lip; vermilion border
66270	Malignant neoplasm of upper lip; external
50296	Malignant neoplasm of upper lip; lipstick area
98740	Malignant neoplasm of upper lip; vermilion border nos
67446	Malignant neoplasm of lower lip; vermilion border
66384	Malignant neoplasm of lower lip; external
95480	Malignant neoplasm of lower lip; lipstick area
101707	Malignant neoplasm of lower lip; vermilion border nos
99493	Malignant neoplasm of upper lip; inner aspect
99001	Malignant neoplasm of upper lip; frenulum
98500	Malignant neoplasm of upper lip; mucosa
90610	Malignant neoplasm of upper lip; oral aspect
100721	Malignant neoplasm of upper lip; inner aspect nos
71147	Malignant neoplasm of lower lip; inner aspect
67504	Malignant neoplasm of lower lip; buccal aspect
91843	Malignant neoplasm of lower lip; frenulum
89909	Malignant neoplasm of lower lip; mucosa
94441	Malignant neoplasm of lower lip; oral aspect
96782	Malignant neoplasm of lower lip; inner aspect nos
61692	Malignant neoplasm of lip unspecified; inner aspect
73614	Malignant neoplasm of lip unspecified; buccal aspect
68399	Malignant neoplasm of lip unspecified; mucosa

100144	Malignant neoplasm of lip; oral aspect
96783	Malignant neoplasm of commissure of lip
18882	Malignant neoplasm of overlapping lesion of lip
37553	Malignant neoplasm of lip; unspecified
100906	Malignant neoplasm of lip; unspecified; external
94251	Malignant neoplasm of lip; unspecified; lipstick area
69761	Malignant neoplasm of lip; vermilion border nos
10283	Malignant neoplasm of tongue
43431	Malignant neoplasm of base of tongue
69671	Malignant neoplasm of posterior third of tongue
34409	Malignant neoplasm of base of tongue dorsal surface
91035	Malignant neoplasm of fixed part of tongue nos
43642	Malignant neoplasm of dorsal surface of tongue
107258	Malignant neoplasm of midline of tongue
43781	Malignant neoplasm of dorsum of tongue nos
36161	Malignant neoplasm of tongue; tip and lateral border
62840	Malignant neoplasm of ventral surface of tongue
102142	Malignant neoplasm of anterior 2/3 of tongue ventral surface
63979	Malignant neoplasm of frenulum linguae
38488	Malignant neoplasm of ventral tongue surface nos
58121	Malignant neoplasm of anterior 2/3 of tongue unspecified
37096	Malignant neoplasm of tongue; junctional zone
24852	Malignant neoplasm of lingual tonsil
47205	Malignant overlapping lesion of tongue
41530	Malignant neoplasm of other sites of tongue
40557	Malignant neoplasm of tongue nos
20292	Malignant neoplasm of major salivary glands
4388	Malignant neoplasm of parotid gland
51786	Malignant neoplasm of submandibular gland
70928	Malignant neoplasm of sublingual gland
70696	Malignant neoplasm of other major salivary glands
50475	Malignant neoplasm of major salivary gland nos
43400	Malignant neoplasm of gum
32024	Malignant neoplasm of upper gum
49360	Malignant neoplasm of lower gum
101753	Malignant neoplasm of other sites of gum
93218	Malignant neoplasm of gum nos
20092	Malignant neoplasm of floor of mouth
45408	Malignant neoplasm of anterior portion of floor of mouth
45986	Malignant neoplasm of lateral portion of floor of mouth
17912	Malignant neoplasm; overlapping lesion of floor of mouth
56709	Malignant neoplasm of other sites of floor of mouth
36716	Malignant neoplasm of floor of mouth nos
14792	Malignant neoplasm of other and unspecified parts of mouth
31364	Malignant neoplasm of cheek mucosa
30402	Malignant neoplasm of buccal mucosa
103796	Malignant neoplasm of vestibule of mouth
95772	Malignant neoplasm of upper buccal sulcus
97530	Malignant neoplasm of lower buccal sulcus
37590	Malignant neoplasm of hard palate
40292	Malignant neoplasm of soft palate
37516	Malignant neoplasm of uvula
70819	Malignant neoplasm of palate unspecified
96003	Malignant neoplasm of junction of hard and soft palate
69951	Malignant neoplasm of roof of mouth
28559	Malignant neoplasm of palate nos

37724	Malignant neoplasm of retromolar area
37916	Malignant neoplasm of other specified mouth parts
55015	Malignant neoplasm of mouth nos
37549	Kaposi's sarcoma of palate
22893	Malignant neoplasm of oropharynx
16241	Malignant neoplasm of tonsil
26448	Malignant neoplasm of faucial tonsil
101988	Malignant neoplasm of palatine tonsil
102151	Malignant neoplasm of overlapping lesion of tonsil
53884	Malignant neoplasm tonsil nos
24397	Malignant neoplasm of tonsillar fossa
55066	Malignant neoplasm of tonsillar pillar
51926	Malignant neoplasm of faucial pillar
99185	Malignant neoplasm of glossopalatine fold
61510	Malignant neoplasm of palatoglossal arch
93842	Malignant neoplasm of palatopharyngeal arch
100002	Malignant neoplasm of tonsillar fossa nos
39554	Malignant neoplasm of vallecula
46728	Malignant neoplasm of anterior epiglottis
26134	Malignant neoplasm of epiglottis; free border
91895	Malignant neoplasm of glossoepiglottic fold
73439	Malignant neoplasm of anterior epiglottis nos
48519	Malignant neoplasm of junctional region of epiglottis
56355	Malignant neoplasm of lateral wall of oropharynx
90124	Malignant neoplasm of posterior wall of oropharynx
67323	Malignant neoplasm of oropharynx; other specified sites
91037	Malignant neoplasm of other specified site of oropharynx nos
43200	Malignant neoplasm of oropharynx nos
24675	Malignant neoplasm of nasopharynx
94390	Malignant neoplasm of roof of nasopharynx
95429	Malignant neoplasm of posterior wall of nasopharynx
33388	Malignant neoplasm of adenoid
46548	Malignant neoplasm of pharyngeal tonsil
96869	Malignant neoplasm of posterior wall of nasopharynx nos
59004	Malignant neoplasm of lateral wall of nasopharynx
37940	Malignant neoplasm of pharyngeal recess
102205	Malignant neoplasm of lateral wall of nasopharynx nos
44139	Malignant neoplasm of anterior wall of nasopharynx
106915	Malignant neoplasm of nasopharyngeal soft palate surface
99386	Malignant neoplasm posterior margin nasal septum and choanae
100918	Malignant neoplasm of anterior wall of nasopharynx nos
66422	Malignant neoplasm; overlapping lesion of nasopharynx
55630	Malignant neoplasm of other specified site of nasopharynx
28665	Malignant neoplasm of nasopharynx nos
34012	Malignant neoplasm of hypopharynx
43548	Malignant neoplasm of postcricoid region
39897	Malignant neoplasm of pyriform sinus
57248	Malignant neoplasm aryepiglottic fold; hypopharyngeal aspect
64462	Malignant neoplasm of posterior pharynx
88362	Malignant neoplasm of other specified hypopharyngeal site
28451	Malignant neoplasm of hypopharynx nos
46114	Malig neop other/ill-defined sites lip; oral cavity; pharynx
16297	Malignant neoplasm of pharynx unspecified
95016	Malignant neoplasm of waldeyer's ring
39084	Malignant neoplasm of laryngopharynx
49758	Malignant neoplasm of other sites lip; oral cavity; pharynx

39430	Malignant neoplasm of lip; oral cavity and pharynx nos
15709	Malignant neoplasm of digestive organs and peritoneum
3357	Carcinoma of digestive organs and peritoneum
1062	Malignant neoplasm of oesophagus
61695	Malignant neoplasm of cervical oesophagus
41362	Malignant neoplasm of thoracic oesophagus
63470	Malignant neoplasm of abdominal oesophagus
50789	Malignant neoplasm of upper third of oesophagus
54171	Malignant neoplasm of middle third of oesophagus
42416	Malignant neoplasm of lower third of oesophagus
67497	Malignant neoplasm; overlapping lesion of oesophagus
53591	Malignant neoplasm of other specified part of oesophagus
30700	Malignant neoplasm of oesophagus nos
4865	Oesophageal cancer
8386	Malignant neoplasm of stomach
32022	Malignant neoplasm of cardia of stomach
100584	Malignant neoplasm of cardiac orifice of stomach
22894	Malignant neoplasm of cardio-oesophageal junction of stomach
94278	Malignant neoplasm of gastro-oesophageal junction
37859	Malignant neoplasm of cardia of stomach nos
21620	Malignant neoplasm of pylorus of stomach
48237	Malignant neoplasm of prepylorus of stomach
41215	Malignant neoplasm of pyloric canal of stomach
59092	Malignant neoplasm of pylorus of stomach nos
19318	Malignant neoplasm of pyloric antrum of stomach
32362	Malignant neoplasm of fundus of stomach
43572	Malignant neoplasm of body of stomach
42193	Malignant neoplasm of lesser curve of stomach unspecified
55434	Malignant neoplasm of greater curve of stomach unspecified
51690	Malignant neoplasm; overlapping lesion of stomach
55019	Malignant neoplasm of other specified site of stomach
65312	Malignant neoplasm of anterior wall of stomach nec
96802	Malignant neoplasm of posterior wall of stomach nec
65372	Malignant neoplasm of other specified site of stomach nos
14800	Malignant neoplasm of stomach nos
6806	Malignant neoplasm of small intestine and duodenum
18613	Malignant neoplasm of duodenum
43479	Malignant neoplasm of jejunum
33871	Malignant neoplasm of ileum
63995	Malignant neoplasm of meckel's diverticulum
66166	Malignant neoplasm; overlapping lesion of small intestine
99896	Malignant neoplasm of other specified site small intestine
43390	Malignant neoplasm of small intestine nos
1220	Malignant neoplasm of colon
9088	Malignant neoplasm of hepatic flexure of colon
6935	Malignant neoplasm of transverse colon
10864	Malignant neoplasm of descending colon
2815	Malignant neoplasm of sigmoid colon
3811	Malignant neoplasm of caecum
22163	Carcinoma of caecum
18632	Malignant neoplasm of appendix
10946	Malignant neoplasm of ascending colon
18619	Malignant neoplasm of splenic flexure of colon
93478	Malignant neoplasm; overlapping lesion of colon
48231	Malignant neoplasm of other specified sites of colon
28163	Malignant neoplasm of colon nos

9118	Colonic cancer
35357	Malignant neoplasm of rectum; rectosigmoid junction and anus
27855	Malignant neoplasm of rectosigmoid junction
1800	Malignant neoplasm of rectum
7219	Carcinoma of rectum
5901	Rectal carcinoma
24370	Malignant neoplasm of anal canal
9491	Anal carcinoma
46159	Malignant neoplasm of cloacogenic zone
27897	Malignant neoplasm of anus unspecified
55659	Malig neop other site rectum; rectosigmoid junction and anus
50974	Malignant neoplasm rectum;rectosigmoid junction and anus nos
8918	Malignant neoplasm of liver and intrahepatic bile ducts
25535	Primary malignant neoplasm of liver
16126	Primary carcinoma of liver
31210	Hepatoblastoma of liver
68410	Primary angiosarcoma of liver
22187	Hepatocellular carcinoma
44399	Primary malignant neoplasm of liver nos
16915	Malignant neoplasm of intrahepatic bile ducts
65124	Malignant neoplasm of interlobular bile ducts
89593	Malignant neoplasm of intrahepatic biliary passages
58088	Malignant neoplasm of intrahepatic gall duct
61643	Malignant neoplasm of intrahepatic bile ducts nos
26393	Malignant neoplasm of liver unspecified
38978	Malignant neoplasm of liver and intrahepatic bile ducts nos
54103	Malignant neoplasm gallbladder and extrahepatic bile ducts
16105	Malignant neoplasm of gallbladder
31393	Carcinoma gallbladder
23433	Malignant neoplasm of extrahepatic bile ducts
72445	Malignant neoplasm of cystic duct
52537	Malignant neoplasm of hepatic duct
7982	Malignant neoplasm of common bile duct
36495	Carcinoma common bile duct
105613	Malignant neoplasm of sphincter of oddi
74896	Malignant neoplasm of extrahepatic bile ducts nos
10949	Malignant neoplasm of ampulla of vater
35039	Malignant neoplasm; overlapping lesion of biliary tract
60312	Malignant neoplasm other gallbladder/extrahepatic bile duct
15907	Malignant neoplasm gallbladder/extrahepatic bile ducts nos
8166	Malignant neoplasm of pancreas
8771	Malignant neoplasm of head of pancreas
40810	Malignant neoplasm of body of pancreas
39870	Malignant neoplasm of tail of pancreas
35535	Malignant neoplasm of pancreatic duct
35795	Malignant neoplasm of islets of langerhans
97875	Malignant neoplasm; overlapping lesion of pancreas
48537	Malignant neoplasm of other specified sites of pancreas
96635	Malignant neoplasm of ectopic pancreatic tissue
95783	Malignant neoplasm of specified site of pancreas nos
34388	Malignant neoplasm of pancreas nos
44108	Malignant neoplasm of retroperitoneum and peritoneum
21330	Malignant neoplasm of retroperitoneum
65159	Malignant neoplasm of perinephric tissue
24048	Malignant neoplasm of retrocaecal tissue
61555	Malignant neoplasm of retroperitoneum nos

17874	Mesothelioma of peritoneum
101907	Overlapping malign lesion of retroperitoneum and peritoneum
46613	Malignant neoplasm of specified parts of peritoneum
59388	Malignant neoplasm of mesocaecum
30165	Malignant neoplasm of mesorectum
50898	Malignant neoplasm of omentum
64516	Malignant neoplasm of parietal peritoneum
39413	Malignant neoplasm of pelvic peritoneum
69821	Malignant neoplasm of the pouch of douglas
90290	Malignant neoplasm of mesentery
64106	Malignant neoplasm of specified parts of peritoneum nos
16298	Malignant neoplasm of retroperitoneum and peritoneum nos
11009	Malig neop oth/ill-defined sites digestive tract/peritoneum
17559	Malignant neoplasm of intestinal tract; part unspecified
11628	Cancer of bowel
65460	Malignant neoplasm of spleen nec
72224	Fibrosarcoma of spleen
93778	Malignant neoplasm of spleen nos
94776	Malignant neoplasm; overlapping lesion of digestive system
56918	Malignant neoplasm other spec digestive tract and peritoneum
51255	Malignant neoplasm of digestive tract and peritoneum nos
34075	Malig neop of respiratory tract and intrathoracic organs
45307	Carcinoma of respiratory tract and intrathoracic organs
26652	Malig neop nasal cavities; middle ear and accessory sinuses
23389	Malignant neoplasm of nasal cavities
71204	Malignant neoplasm of cartilage of nose
98911	Malignant neoplasm of nasal conchae
62761	Malignant neoplasm of septum of nose
62182	Malignant neoplasm of vestibule of nose
42856	Malignant neoplasm of nasal cavities nos
24456	Malig neop auditory tube; middle ear and mastoid air cells
107916	Malignant neoplasm of auditory (eustachian) tube
98537	Malignant neoplasm of tympanic cavity
54613	Malignant neoplasm of tympanic antrum
71946	Malignant neoplasm of mastoid air cells
73537	Malig neop auditory tube; middle ear; mastoid air cells nos
32174	Malignant neoplasm of maxillary sinus
54636	Malignant neoplasm of ethmoid sinus
15684	Malignant neoplasm of frontal sinus
65215	Malignant neoplasm of sphenoidal sinus
39590	Malignant neoplasm; overlapping lesion of accessory sinuses
96971	Malig neop other site nasal cavity; middle ear and sinuses
55246	Malignant neoplasm of accessory sinus nos
319	Malignant neoplasm of larynx
318	Malignant neoplasm of glottis
26165	Malignant neoplasm of supraglottis
22441	Malignant neoplasm of subglottis
43111	Malignant neoplasm of laryngeal cartilage
63460	Malignant neoplasm of arytenoid cartilage
37805	Malignant neoplasm of cricoid cartilage
107878	Malignant neoplasm of cuneiform cartilage
47862	Malignant neoplasm of thyroid cartilage
97332	Malignant neoplasm of laryngeal cartilage nos
50579	Malignant neoplasm; overlapping lesion of larynx
55374	Malignant neoplasm of epiglottis nos
26813	Malignant neoplasm of larynx; other specified site

9237	Malignant neoplasm of larynx nos
13243	Malignant neoplasm of trachea; bronchus and lung
15221	Malignant neoplasm of trachea
103946	Malignant neoplasm of mucosa of trachea
37810	Malignant neoplasm of trachea nos
12870	Malignant neoplasm of main bronchus
17391	Malignant neoplasm of carina of bronchus
33444	Malignant neoplasm of hilus of lung
21698	Malignant neoplasm of main bronchus nos
10358	Malignant neoplasm of upper lobe; bronchus or lung
20170	Pancoast's syndrome
31700	Malignant neoplasm of upper lobe bronchus
25886	Malignant neoplasm of upper lobe of lung
44169	Malignant neoplasm of upper lobe; bronchus or lung nos
31268	Malignant neoplasm of middle lobe; bronchus or lung
41523	Malignant neoplasm of middle lobe bronchus
39923	Malignant neoplasm of middle lobe of lung
54134	Malignant neoplasm of middle lobe; bronchus or lung nos
31188	Malignant neoplasm of lower lobe; bronchus or lung
18678	Malignant neoplasm of lower lobe bronchus
12582	Malignant neoplasm of lower lobe of lung
42566	Malignant neoplasm of lower lobe; bronchus or lung nos
36371	Malignant neoplasm of overlapping lesion of bronchus & lung
7484	Mesothelioma
38961	Malignant neoplasm of other sites of bronchus or lung
3903	Malignant neoplasm of bronchus or lung nos
2587	Lung cancer
31573	Malignant neoplasm of pleura
67107	Malignant neoplasm of parietal pleura
106194	Malignant neoplasm of visceral pleura
9600	Mesothelioma of pleura
98104	Malignant neoplasm of other specified pleura
34742	Malignant neoplasm of pleura nos
62556	Malignant neoplasm of thymus; heart and mediastinum
27483	Malignant neoplasm of thymus
95644	Malignant neoplasm of heart
63430	Malignant neoplasm of endocardium
65605	Malignant neoplasm of myocardium
94975	Malignant neoplasm of pericardium
101885	Mesothelioma of pericardium
50289	Malignant neoplasm of heart nos
27715	Malignant neoplasm of anterior mediastinum
92720	Malignant neoplasm of posterior mediastinum
61064	Malignant neoplasm of mediastinum; part unspecified
100232	Malig neop of other site of heart; thymus and mediastinum
66750	Malignant neoplasm of heart; thymus and mediastinum nos
39531	Malig neo; overlapping lesion of heart; mediastinum & pleura
66646	Malignant neoplasm; overlap lesion of resp & intrathor orgs
44356	Malig neop other/ill-defined sites resp/intrathoracic organs
65793	Malig neop of upper respiratory tract; part unspecified
29283	Malignant neoplasm of other site of respiratory tract
42569	Malignant neoplasm of respiratory tract nos
18608	Malig neop of bone; connective tissue; skin and breast
9902	Carcinoma of bone; connective tissue; skin and breast
12539	Sarcoma of bone and connective tissue
18314	Malignant neoplasm of bone and articular cartilage

59036	Malignant neoplasm of bones of skull and face
53594	Malignant neoplasm of ethmoid bone
53599	Malignant neoplasm of frontal bone
59520	Malignant neoplasm of malar bone
95458	Malignant neoplasm of nasal bone
55953	Malignant neoplasm of occipital bone
50298	Malignant neoplasm of orbital bone
54747	Malignant neoplasm of parietal bone
55595	Malignant neoplasm of sphenoid bone
62104	Malignant neoplasm of temporal bone
50299	Malignant neoplasm of zygomatic bone
17475	Malignant neoplasm of maxilla
44452	Malignant neoplasm of vomer
69146	Malignant neoplasm of bones of skull and face nos
33833	Malignant neoplasm of mandible
16704	Malignant neoplasm of vertebral column
46939	Malignant neoplasm of cervical vertebra
32372	Malignant neoplasm of thoracic vertebra
54691	Malignant neoplasm of lumbar vertebra
49701	Malignant neoplasm of vertebral column nos
27528	Malignant neoplasm of ribs; sternum and clavicle
37842	Malignant neoplasm of rib
49491	Malignant neoplasm of sternum
66639	Malignant neoplasm of clavicle
60403	Malignant neoplasm of costal cartilage
67763	Malignant neoplasm of costo-vertebral joint
54493	Malignant neoplasm of xiphoid process
51237	Malignant neoplasm of rib; sternum and clavicle nos
71810	Malignant neoplasm of scapula and long bones of upper arm
49054	Malignant neoplasm of scapula
105797	Malignant neoplasm of acromion
61741	Malignant neoplasm of humerus
92371	Malignant neoplasm of radius
64848	Malignant neoplasm of ulna
65880	Malig neop of scapula and long bones of upper arm nos
73530	Malignant neoplasm of hand bones
106069	Malignant neoplasm of carpal bones
72464	Malignant neoplasm of metacarpal bones
57988	Malignant neoplasm of carpal bone - scaphoid
69104	Malignant neoplasm of carpal bone - lunate
94427	Malignant neoplasm of fifth metacarpal bone
86812	Malignant neoplasm of phalanges of hand
73556	Malignant neoplasm of hand bones nos
54631	Malignant neoplasm of pelvic bones; sacrum and coccyx
44609	Malignant neoplasm of ilium
59223	Malignant neoplasm of ischium
51921	Malignant neoplasm of pubis
40966	Malignant neoplasm of sacral vertebra
66908	Malignant neoplasm of coccygeal vertebra
50152	Malignant sacral teratoma
38938	Malignant neoplasm of pelvis; sacrum or coccyx nos
68055	Malignant neoplasm of long bones of leg
56513	Malignant neoplasm of femur
50402	Malignant neoplasm of fibula
40814	Malignant neoplasm of tibia
62630	Malignant neoplasm of long bones of leg nos

105475	Malignant neoplasm of short bones of leg
95182	Malignant neoplasm of talus
72212	Malignant neoplasm of calcaneum
34878	Malignant neoplasm of medial cuneiform
69927	Malignant neoplasm of first metatarsal bone
58949	Malignant neoplasm of phalanges of foot
103354	Malignant neoplasm of short bones of leg nos
67451	Malignant neoplasm/overlap lesion/bone??? Cartilage
43614	Malignant neoplasm/bones??? Cartilage/limb;unspfd
16075	Malignant neoplasm of bone and articular cartilage nos
19437	Osteosarcoma
34451	Malignant neoplasm of connective and other soft tissue
43475	Malig neop of connective and soft tissue head; face and neck
59382	Malignant neoplasm of soft tissue of head
40014	Malignant neoplasm of soft tissue of face
48517	Malignant neoplasm of soft tissue of neck
60035	Malignant neoplasm of cartilage of ear
49463	Malignant neoplasm of tarsus of eyelid
108389	Malignant neoplasm soft tissues of cervical spine
73718	Malig neop connective and soft tissue head; face; neck nos
53989	Malig neop connective and soft tissue upper limb/shoulder
50222	Malignant neoplasm of connective and soft tissue of shoulder
64345	Malignant neoplasm of connective and soft tissue; upper arm
57482	Malignant neoplasm of connective and soft tissue of fore-arm
19321	Malignant neoplasm of connective and soft tissue of hand
91586	Malignant neoplasm of connective and soft tissue of finger
63988	Malignant neoplasm of connective and soft tissue of thumb
104913	Malig neop connective soft tissue upper limb/shoulder nos
66088	Malig neop of connective and soft tissue of hip and leg
102949	Malignant neoplasm of connective and soft tissue of hip
44805	Malig neop of connective and soft tissue thigh and upper leg
54965	Malig neop connective and soft tissue of popliteal space
30542	Malig neop of connective and soft tissue of lower leg
54222	Malignant neoplasm of connective and soft tissue of foot
99572	Malignant neoplasm of connective and soft tissue of toe
90546	Malig neop connective and soft tissue hip and leg nos
22290	Malignant neoplasm of connective and soft tissue of thorax
29160	Malignant neoplasm of connective and soft tissue of axilla
54186	Malignant neoplasm of diaphragm
72522	Malignant neoplasm of great vessels
104139	Malig neoplasm of connective and soft tissues of thor spine
98408	Malig neop of connective and soft tissue of thorax nos
45071	Malignant neoplasm of connective and soft tissue of abdomen
66488	Malig neop of connective and soft tissue of abdominal wall
94272	Malig neoplasm of connective and soft tissues of lumb spine
60247	Malig neop of connective and soft tissue of abdomen nos
51965	Malignant neoplasm of connective and soft tissue of pelvis
70463	Malignant neoplasm of connective and soft tissue of buttock
67324	Malig neop of connective and soft tissue of inguinal region
59152	Malignant neoplasm of connective and soft tissue of perineum
58836	Malig neop of connective and soft tissue of pelvis nos
57471	Malig neop of connective and soft tissue trunk unspecified
65233	Malig neop connective and soft tissue other specified site
15182	Malignant neoplasm of connective and soft tissue; site nos
104128	Kaposi's sarcoma of soft tissue
865	Malignant melanoma of skin

70637	Malignant melanoma of lip
54632	Malignant melanoma of eyelid including canthus
57260	Malignant melanoma of ear and external auricular canal
59061	Malignant melanoma of auricle (ear)
102145	Malignant melanoma of external auditory meatus
73744	Malignant melanoma of ear and external auricular canal nos
47252	Malignant melanoma of other and unspecified parts of face
41278	Malignant melanoma of external surface of cheek
71136	Malignant melanoma of chin
47094	Malignant melanoma of eyebrow
68133	Malignant melanoma of forehead
45139	Malignant melanoma of external surface of nose
58958	Malignant melanoma of temple
67806	Malignant melanoma of face nos
65625	Malignant melanoma of scalp and neck
55881	Malignant melanoma of scalp
45306	Malignant melanoma of neck
99257	Malignant melanoma of scalp and neck nos
38689	Malignant melanoma of trunk (excluding scrotum)
49814	Malignant melanoma of axilla
32768	Malignant melanoma of breast
53629	Malignant melanoma of buttock
34259	Malignant melanoma of groin
95629	Malignant melanoma of perineum
43715	Malignant melanoma of umbilicus
43463	Malignant melanoma of back
51209	Malignant melanoma of chest wall
45760	Malignant melanoma of trunk; excluding scrotum; nos
65164	Malignant melanoma of upper limb and shoulder
50505	Malignant melanoma of shoulder
54685	Malignant melanoma of upper arm
45755	Malignant melanoma of fore-arm
62475	Malignant melanoma of hand
25602	Malignant melanoma of finger
63997	Malignant melanoma of thumb
55292	Malignant melanoma of upper limb or shoulder nos
46255	Malignant melanoma of lower limb and hip
73536	Malignant melanoma of hip
51873	Malignant melanoma of thigh
54305	Malignant melanoma of knee
39878	Malignant melanoma of popliteal fossa area
37872	Malignant melanoma of lower leg
42714	Malignant melanoma of ankle
61246	Malignant melanoma of heel
41490	Malignant melanoma of foot
36899	Malignant melanoma of toe
53369	Malignant melanoma of great toe
64327	Malignant melanoma of lower limb or hip nos
42153	Malignant melanoma of other specified skin site
96585	Overlapping malignant melanoma of skin
28556	Malignant melanoma of skin nos
4632	Other malignant neoplasm of skin
37016	Malignant neoplasm of sebaceous gland
40443	Malignant neoplasm of sweat gland
18245	Malignant neoplasm of skin of lip
43087	Malignant neoplasm of eyelid including canthus

36731	Malignant neoplasm of canthus
55550	Malignant neoplasm of upper eyelid
41958	Malignant neoplasm of lower eyelid
53515	Malignant neoplasm skin of ear and external auricular canal
33997	Malignant neoplasm of skin of auricle (ear)
62080	Malignant neoplasm of skin of external auditory meatus
33271	Malignant neoplasm of pinna nec
62399	Malig neop skin of ear and external auricular canal nos
27370	Malignant neoplasm skin of other and unspecified parts face
30645	Malignant neoplasm of skin of cheek; external
49403	Malignant neoplasm of skin of chin
55670	Malignant neoplasm of skin of eyebrow
30576	Malignant neoplasm of skin of forehead
16202	Malignant neoplasm of skin of nose (external)
21327	Malignant neoplasm of skin of temple
46008	Malignant neoplasm skin other and unspec part of face nos
54234	Malignant neoplasm of scalp and skin of neck
37165	Malignant neoplasm of scalp
43619	Malignant neoplasm of skin of neck
73760	Malignant neoplasm of scalp or skin of neck nos
57446	Malignant neoplasm of skin of trunk; excluding scrotum
70380	Malignant neoplasm of skin of axillary fold
37969	Malignant neoplasm of skin of chest; excluding breast
30543	Malignant neoplasm of skin of breast
18618	Malignant neoplasm of skin of abdominal wall
67748	Malignant neoplasm of skin of umbilicus
66319	Malignant neoplasm of skin of groin
46458	Malignant neoplasm of skin of perineum
45077	Malignant neoplasm of skin of back
62305	Malignant neoplasm of skin of buttock
23480	Malignant neoplasm of perianal skin
66447	Malignant neoplasm of skin of scapular region
15868	Malignant neoplasm of skin of trunk; excluding scrotum; nos
30747	Malignant neoplasm of skin of upper limb and shoulder
43122	Malignant neoplasm of skin of shoulder
42707	Malignant neoplasm of skin of upper arm
30577	Malignant neoplasm of skin of fore-arm
54352	Malignant neoplasm of skin of hand
25245	Malignant neoplasm of skin of finger
64406	Malignant neoplasm of skin of thumb
60526	Malignant neoplasm of skin of upper limb or shoulder nos
57442	Malignant neoplasm of skin of lower limb and hip
70988	Malignant neoplasm of skin of hip
58601	Malignant neoplasm of skin of thigh
56954	Malignant neoplasm of skin of knee
68197	Malignant neoplasm of skin of popliteal fossa area
33682	Malignant neoplasm of skin of lower leg
64270	Malignant neoplasm of skin of ankle
104025	Malignant neoplasm of skin of heel
70587	Malignant neoplasm of skin of foot
65782	Malignant neoplasm of skin of toe
67914	Malignant neoplasm of skin of great toe
61194	Malignant neoplasm of skin of lower limb or hip nos
24375	Dermatofibrosarcoma protuberans
42429	Malignant neoplasm overlapping lesion of skin
18354	Malignant neoplasm of other specified skin sites

2492	Malignant neoplasm of skin nos
27931	Kaposi's sarcoma of skin
3968	Malignant neoplasm of female breast
348	Ca female breast
26853	Malignant neoplasm of nipple and areola of female breast
23380	Malignant neoplasm of nipple of female breast
64686	Malignant neoplasm of areola of female breast
59831	Malignant neoplasm of nipple or areola of female breast nos
31546	Malignant neoplasm of central part of female breast
29826	Malignant neoplasm of upper-inner quadrant of female breast
45222	Malignant neoplasm of lower-inner quadrant of female breast
23399	Malignant neoplasm of upper-outer quadrant of female breast
42070	Malignant neoplasm of lower-outer quadrant of female breast
20685	Malignant neoplasm of axillary tail of female breast
49148	Malignant neoplasm; overlapping lesion of breast
56715	Malignant neoplasm of other site of female breast
95057	Malignant neoplasm of ectopic site of female breast
38475	Malignant neoplasm of other site of female breast nos
9470	Malignant neoplasm of female breast nos
19423	Malignant neoplasm of male breast
54494	Malignant neoplasm of nipple and areola of male breast
68480	Malignant neoplasm of nipple of male breast
67884	Malignant neoplasm of areola of male breast
54202	Malignant neoplasm of other site of male breast
95323	Malignant neoplasm of ectopic site of male breast
48809	Malignant neoplasm of male breast nos
19389	Malig neop of bone; connective tissue; skin and breast os
41011	Malig neop of bone; connective tissue; skin and breast nos
13252	Malignant neoplasm of genitourinary organ
16874	Carcinoma of genitourinary organ
2744	Malignant neoplasm of uterus; part unspecified
2747	Malignant neoplasm of cervix uteri
3230	Cervical carcinoma (uterus)
48820	Malignant neoplasm of endocervix
57235	Malignant neoplasm of endocervical canal
53103	Malignant neoplasm of endocervical gland
50285	Malignant neoplasm of endocervix nos
50297	Malignant neoplasm of exocervix
58094	Malignant neoplasm; overlapping lesion of cervix uteri
32955	Malignant neoplasm of other site of cervix
95505	Malignant neoplasm of cervical stump
57719	Malignant neoplasm of squamocolumnar junction of cervix
43435	Malignant neoplasm of other site of cervix nos
28311	Malignant neoplasm of cervix uteri nos
93762	Malignant neoplasm of placenta
28003	Choriocarcinoma
7046	Malignant neoplasm of body of uterus
3213	Malignant neoplasm of corpus uteri; excluding isthmus
72723	Malignant neoplasm of cornu of corpus uteri
68155	Malignant neoplasm of fundus of corpus uteri
2890	Malignant neoplasm of endometrium of corpus uteri
49400	Malignant neoplasm of endometrium
45793	Malignant neoplasm of myometrium of corpus uteri
45490	Malignant neoplasm of corpus uteri nos
43940	Malignant neoplasm of isthmus of uterine body
59097	Malignant neoplasm of lower uterine segment

70729	Malignant neoplasm of isthmus of uterine body nos
16967	Malignant neoplasm of overlapping lesion of corpus uteri
31608	Malignant neoplasm of other site of uterine body
33617	Malignant neoplasm of body of uterus nos
19141	Malignant neoplasm of ovary and other uterine adnexa
7805	Malignant neoplasm of ovary
1986	Cancer of ovary
49828	Malignant neoplasm of fallopian tube
101778	Malignant neoplasm of broad ligament
46153	Malignant neoplasm of parametrium
97996	Malignant neoplasm of other site of uterine adnexa
65106	Malignant neoplasm of uterine adnexa nos
4555	Malig neop of other and unspecified female genital organs
37328	Malignant neoplasm of vagina
10698	Malignant neoplasm of vaginal vault
60772	Malignant neoplasm of vagina nos
43761	Malignant neoplasm of labia majora
47899	Malignant neoplasm of greater vestibular (bartholin's) gland
59362	Malignant neoplasm of labia majora nos
58061	Malignant neoplasm of labia minora
53910	Malignant neoplasm of clitoris
4554	Malignant neoplasm of vulva unspecified
11991	Primary vulval cancer
26454	Malignant neoplasm/overlapping lesion/feml genital organs
95421	Malignant neoplasm of other specified female genital organ
27617	Malignant neoplasm of overlapping lesion of vulva
20166	Malignant neoplasm of female genital organ nos
780	Malignant neoplasm of prostate
15148	Malignant neoplasm of testis
64602	Malignant neoplasm of undescended testis
7740	Seminoma of undescended testis
96429	Malignant neoplasm of undescended testis nos
19475	Malignant neoplasm of descended testis
21786	Seminoma of descended testis
38510	Malignant neoplasm of testis nos
2961	Seminoma of testis
3541	Malignant neoplasm of penis and other male genital organs
50681	Malignant neoplasm of prepuce (foreskin)
17841	Malignant neoplasm of glans penis
48743	Malignant neoplasm of body of penis
43392	Malignant neoplasm of penis; part unspecified
72127	Malignant neoplasm of epididymis
63331	Malignant neoplasm of spermatic cord
47767	Malignant neoplasm of scrotum
52570	Malignant neoplasm; overlapping lesion of penis
67949	Malignant neoplasm of other male genital organ
68161	Malignant neoplasm of seminal vesicle
47668	Malignant neoplasm of tunica vaginalis
68824	Malignant neoplasm; overlapping lesion male genital orgs
92329	Malignant neoplasm of other male genital organ nos
63224	Malignant neoplasm of penis and other male genital organ nos
779	Malignant neoplasm of urinary bladder
38862	Malignant neoplasm of trigone of urinary bladder
44996	Malignant neoplasm of dome of urinary bladder
35963	Malignant neoplasm of lateral wall of urinary bladder
19162	Malignant neoplasm of anterior wall of urinary bladder

42012	Malignant neoplasm of posterior wall of urinary bladder
41571	Malignant neoplasm of bladder neck
28241	Malignant neoplasm of ureteric orifice
42023	Malignant neoplasm of urachus
36949	Malignant neoplasm of other site of urinary bladder
47801	Malignant neoplasm; overlapping lesion of bladder
31102	Malignant neoplasm of urinary bladder nos
13559	Malig neop of kidney and other unspecified urinary organs
18712	Renal malignant neoplasm
1599	Malignant neoplasm of kidney parenchyma
7978	Hypernephroma
12389	Malignant neoplasm of renal pelvis
27540	Malignant neoplasm of renal calyces
101608	Malignant neoplasm of ureteropelvic junction
54184	Malignant neoplasm of renal pelvis nos
15223	Malignant neoplasm of ureter
15644	Malignant neoplasm of urethra
72174	Malignant neoplasm of paraurethral glands
44884	Malignant neoplasm of other urinary organs
59286	Malignant neoplasm of overlapping lesion of urinary organs
29462	Malignant neoplasm of kidney or urinary organs nos
38931	Malignant neoplasm of genitourinary organ os
52594	Malignant neoplasm of genitourinary organ nos
10995	Malignant neoplasm of other and unspecified sites
8693	Carcinoma of other and unspecified sites
20160	Malignant neoplasm of eye
98813	Malig neop eyeball excl conjunctiva; cornea; retina; choroid
59041	Malignant neoplasm of ciliary body
59381	Malignant neoplasm of iris
106569	Malignant neoplasm of crystalline lens
56718	Malignant neoplasm of eyeball nos
45667	Malignant neoplasm of orbit
86996	Malignant neoplasm of connective tissue of orbit
63104	Malignant neoplasm of orbit nos
64817	Malignant neoplasm of lacrimal gland
63657	Malignant neoplasm of conjunctiva
73992	Malignant neoplasm of cornea
28069	Malignant neoplasm of retina
15991	Malignant neoplasm of choroid
71584	Malignant neoplasm of lacrimal duct
101805	Malignant neoplasm of lacrimal sac
65357	Malignant neoplasm of nasolacrimal duct
45922	Malignant neoplasm; overlapping lesion of eye and adnexa
40437	Malignant neoplasm of other specified site of eye
54956	Malignant neoplasm of eye nos
18617	Malignant neoplasm of brain
10851	Cerebral tumour - malignant
15711	Malignant neoplasm cerebrum (excluding lobes and ventricles)
48073	Malignant neoplasm of basal ganglia
61399	Malignant neoplasm of cerebral cortex
99913	Malignant neoplasm of globus pallidus
70942	Malignant neoplasm of hypothalamus
62126	Malignant neoplasm of thalamus
54133	Malignant neoplasm of cerebrum nos
42426	Malignant neoplasm of frontal lobe
46792	Malignant neoplasm of temporal lobe

67236	Malignant neoplasm of hippocampus
47556	Malignant neoplasm of temporal lobe nos
19226	Malignant neoplasm of parietal lobe
39088	Malignant neoplasm of occipital lobe
52511	Malignant neoplasm of cerebral ventricles
46789	Malignant neoplasm of choroid plexus
45154	Malignant neoplasm of cerebellum
44089	Malignant neoplasm of brain stem
64557	Malignant neoplasm of cerebral peduncle
49132	Malignant neoplasm of medulla oblongata
93537	Malignant neoplasm of midbrain
91240	Malignant neoplasm of pons
68641	Malignant neoplasm of brain stem nos
71139	Malignant neoplasm of other parts of brain
59170	Malignant neoplasm of corpus callosum
65241	Malignant neoplasm; overlapping lesion of brain
100733	Malignant neoplasm of other part of brain nos
41520	Malignant neoplasm of brain nos
65458	Malig neop of other and unspecified parts of nervous system
99621	Malignant neoplasm of cranial nerves
64971	Malignant neoplasm of olfactory bulb
70126	Malignant neoplasm of optic nerve
65599	Malignant neoplasm of acoustic nerve
101086	Malignant neoplasm of cranial nerves nos
28919	Malignant neoplasm of cerebral meninges
70104	Malignant neoplasm of cerebral meninges nos
51115	Malignant neoplasm of spinal cord
49714	Malignant neoplasm of spinal meninges
67211	Malignant neoplasm of spinal meninges nos
24235	Malig neopl peripheral nerves and autonomic nervous system
63568	Malignant neoplasm of peripheral nerves of head; face & neck
61716	Malignant neoplasm of peripheral nerve;upp limb;incl should
89258	Malignant neoplasm of peripheral nerve of low limb; incl hip
63695	Malignant neoplasm of peripheral nerve of thorax
86046	Malignant neoplasm of peripheral nerve of abdomen
73988	Malignant neoplasm of peripheral nerve of pelvis
50777	Malignant neoplasm;overlap lesion periph nerve & auton ns
106654	Mal neoplasm/periph nerves??? Nervous system;unspc
9622	Malignant neoplasm of cauda equina
53504	Malig neopl; overlap lesion brain & other part of cns
49875	Malignant neoplasm of meninges; unspecified
88144	Malignant neoplasm of other specified part of nervous system
56490	Malignant neoplasm of nervous system nos
5637	Malignant neoplasm of thyroid gland
30511	Malig neop of other endocrine glands and related structures
28148	Malignant neoplasm of adrenal gland
61390	Malignant neoplasm of adrenal cortex
94220	Malignant neoplasm of adrenal medulla
70824	Malignant neoplasm of adrenal gland nos
4218	Malignant neoplasm of parathyroid gland
59823	Malignant neoplasm pituitary gland and craniopharyngeal duct
8550	Malignant neoplasm of pituitary gland
39899	Malignant neoplasm of craniopharyngeal duct
59718	Malig neop pituitary gland or craniopharyngeal duct nos
42460	Malignant neoplasm of pineal gland
57047	Malignant neoplasm of carotid body

50035	Malignant neoplasm of aortic body and other paraganglia
51795	Malignant neoplasm of glomus jugulare
47840	Malignant neoplasm of aortic body
46905	Malignant neoplasm of coccygeal body
103995	Malignant neoplasm of aortic body or paraganglia nos
87113	Malignant neoplasm-pluriglandular involvement;unspecified
90659	Malignant neoplasm of other specified endocrine gland
64195	Malig neop of endocrine gland or related structure nos
9030	Malignant neoplasm of other and ill-defined sites
68236	Malignant neoplasm of head; neck and face
55098	Malignant neoplasm of head nos
41931	Malignant neoplasm of cheek nos
12490	Malignant neoplasm of nose nos
51818	Malignant neoplasm of jaw nos
16280	Malignant neoplasm of neck nos
73510	Malignant neoplasm of supraclavicular fossa nos
58903	Malignant neoplasm of head; neck and face nos
47286	Malignant neoplasm of thorax
37618	Malignant neoplasm of axilla nos
23861	Malignant neoplasm of chest wall nos
97547	Malignant neoplasm of intrathoracic site nos
64810	Malignant neoplasm of thorax nos
15976	Malignant neoplasm of abdomen
52316	Malignant neoplasm of pelvis
57854	Malignant neoplasm of inguinal region nos
89916	Malignant neoplasm of presacral region
107126	Malignant neoplasm of sacrococcygeal region
55101	Malignant neoplasm of pelvis nos
27449	Malignant neoplasm of upper limb nos
31399	Malignant neoplasm of lower limb nos
42218	Malignant neoplasm of other specified sites
68787	Malignant neoplasm of back nos
67217	Malignant neoplasm of trunk nos
94355	Malignant neoplasm of flank nos
60052	Malignant neoplasm of specified site nos
45267	Malignant neoplasm of other and ill defined site nos
47810	Malignant neoplasm of unspecified site
49525	Kaposi's sarcoma; unspecified
38736	Malignant neoplasm of other and unspecified site os
1056	Malignant neoplasm of other and unspecified site nos
12323	Malignant neoplasm of lymphatic and haemopoietic tissue
37112	Malignant neoplasm of histiocytic tissue
41369	Lymphosarcoma and reticulosarcoma
1481	Reticulosarcoma
60242	Reticulosarcoma of unspecified site
71031	Reticulosarcoma of lymph nodes of head; face and neck
70374	Reticulosarcoma of intra-abdominal lymph nodes
95058	Reticulosarcoma of spleen
99240	Reticulosarcoma nos
27416	Lymphosarcoma
71625	Lymphosarcoma of unspecified site
71238	Lymphosarcoma of lymph nodes of head; face and neck
62380	Lymphosarcoma of intrathoracic lymph nodes
64670	Lymphosarcoma of intra-abdominal lymph nodes
100352	Lymphosarcoma of lymph nodes of inguinal region and leg
103245	Lymphosarcoma of spleen

104790	Lymphosarcoma of lymph nodes of multiple sites
63723	Lymphosarcoma nos
21402	Burkitt's lymphoma
59115	Burkitt's lymphoma of lymph nodes of head; face and neck
100006	Burkitt's lymphoma of intrathoracic lymph nodes
97577	Burkitt's lymphoma of intra-abdominal lymph nodes
92380	Burkitt's lymphoma of lymph nodes of inguinal region and leg
71304	Burkitt's lymphoma nos
99887	Other specified reticulosarcoma or lymphosarcoma
99951	Reticulosarcoma or lymphosarcoma nos
2462	Hodgkin's disease
65489	Hodgkin's paragranuloma
100423	Hodgkin's paragranuloma of lymph nodes of head; face; neck
98840	Hodgkin's paragranuloma of intra-abdominal lymph nodes
44196	Hodgkin's granuloma
98909	Hodgkin's granuloma of lymph nodes of head; face and neck
64036	Hodgkin's sarcoma
68039	Hodgkin's sarcoma of lymph nodes of axilla and upper limb
38939	Hodgkin's disease; lymphocytic-histiocytic predominance
71142	Hodgkin's; lymphocytic-histiocytic predominance unspec site
68330	Hodgkin's; lymphocytic-histiocytic pred of head; face; neck
92245	Hodgkin's; lymphocytic-histiocytic pred intrathoracic nodes
73532	Hodgkin's; lymphocytic-histiocytic pred intra-abdominal node
93951	Hodgkin's; lymphocytic-histiocytic pred inguinal and leg
95338	Hodgkin's; lymphocytic-histiocytic pred intrapelvic nodes
106911	Hodgkin's; lymphocytic-histiocytic predominance of spleen
104743	Hodgkin's; lymphocytic-histiocytic pred of multiple sites
29876	Hodgkin's; lymphocytic-histiocytic predominance nos
29178	Hodgkin's disease; nodular sclerosis
57225	Hodgkin's disease; nodular sclerosis of unspecified site
55303	Hodgkin's nodular sclerosis of head; face and neck
67506	Hodgkin's nodular sclerosis of intrathoracic lymph nodes
61149	Hodgkin's nodular sclerosis of intra-abdominal lymph nodes
65483	Hodgkin's nodular sclerosis of lymph nodes of axilla and arm
105472	Hodgkin's disease; nodular sclerosis of spleen
19140	Hodgkin's nodular sclerosis of lymph nodes of multiple sites
63054	Hodgkin's disease; nodular sclerosis nos
49605	Hodgkin's disease; mixed cellularity
97863	Hodgkin's disease; mixed cellularity of unspecified site
94407	Hodgkin's mixed cellularity of lymph nodes head; face; neck
58684	Hodgkin's mixed cellularity of intrathoracic lymph nodes
94005	Hodgkin's disease; mixed cellularity nos
67703	Hodgkin's disease; lymphocytic depletion
95049	Hodgkin's lymphocytic depletion of unspecified site
63625	Hodgkin's lymphocytic depletion lymph nodes axilla and arm
101715	Hodgkin's disease; lymphocytic depletion of spleen
107032	Hodgkin's lymphocytic depletion lymph nodes multiple sites
101530	Hodgkin's disease; lymphocytic depletion nos
53397	Hodgkin's disease nos
61662	Hodgkin's disease nos; unspecified site
59778	Hodgkin's disease nos of lymph nodes of head; face and neck
59755	Hodgkin's disease nos of intrathoracic lymph nodes
107804	Hodgkin's disease nos of intra-abdominal lymph nodes
91900	Hodgkin's disease nos of lymph nodes of axilla and arm
99012	Hodgkin's disease nos of lymph nodes inguinal region and leg
94279	Hodgkin's disease nos of spleen

97746	Hodgkin's disease nos of lymph nodes of multiple sites
42461	Hodgkin's disease nos
33333	Other malignant neoplasm of lymphoid and histiocytic tissue
5179	Nodular lymphoma (brill - symmers disease)
66327	Nodular lymphoma of unspecified site
45264	Nodular lymphoma of lymph nodes of head; face and neck
105203	Nodular lymphoma of intrathoracic lymph nodes
92068	Nodular lymphoma of intra-abdominal lymph nodes
94995	Nodular lymphoma of lymph nodes of inguinal region and leg
58082	Nodular lymphoma of lymph nodes of multiple sites
65701	Nodular lymphoma nos
12006	Mycosis fungoides
95949	Mycosis fungoides of unspecified site
91674	Mycosis fungoides of intra-abdominal lymph nodes
96379	Mycosis fungoides of lymph nodes of axilla and upper limb
72714	Mycosis fungoides of lymph nodes of inguinal region and leg
95012	Mycosis fungoides of lymph nodes of multiple sites
38005	Mycosis fungoides nos
35014	Sezary's disease
100532	Sezary's disease nos
44267	Malignant histiocytosis
69497	Malignant histiocytosis of unspecified site
94415	Malignant histiocytosis of lymph nodes head; face and neck
65642	Malignant histiocytosis of intra-abdominal lymph nodes
58871	Malignant histiocytosis nos
27330	Leukaemic reticuloendotheliosis
5137	Leukaemic reticuloendotheliosis
65122	Leukaemic reticuloendotheliosis of unspecified sites
65123	Leukaemic reticuloend of intra-abdominal lymph nodes
73777	Leukaemic reticuloendotheliosis nos
34926	Letterer-siwe disease
4870	Histiocytosis x (acute; progressive)
102715	Letterer-siwe disease of unspecified sites
102158	Letterer-siwe disease of intrathoracic lymph nodes
54083	Letterer-siwe disease of lymph nodes of multiple sites
47204	Letterer-siwe disease nos
15036	Malignant mast cell tumours
103900	Mast cell malignancy of unspecified site
100615	Mast cell malignancy of lymph nodes inguinal region and leg
31324	Mast cell malignancy of lymph nodes of multiple sites
89657	Malignant mast cell tumour nos
3604	Non - hodgkin's lymphoma
28639	Follicular non-hodgkin's small cleaved cell lymphoma
70842	Follicular non-hodg mixed sml cleavd & lge cell lymphoma
49262	Follicular non-hodgkin's large cell lymphoma
50668	Diffuse non-hodgkin's small cell (diffuse) lymphoma
108182	Diffuse non-hodgkin's small cleaved cell (diffuse) lymphoma
50695	Diffuse non-hodgkin mixed sml & lge cell (diffuse) lymphoma
53551	Diffuse non-hodgkin's immunoblastic (diffuse) lymphoma
17460	Diffuse non-hodgkin's lymphoblastic (diffuse) lymphoma
65180	Diffuse non-hodgkin's lymphoma undifferentiated (diffuse)
31576	Other types of follicular non-hodgkin's lymphoma
21549	Follicular non-hodgkin's lymphoma
17182	Follicular lymphoma nos
70509	Diffuse non-hodgkin's centroblastic lymphoma
31794	Unspecified b-cell non-hodgkin's lymphoma

39798	Diffuse non-hodgkin's lymphoma; unspecified
17887	Malignant lymphoma otherwise specified
90201	T-zone lymphoma
57737	Lymphoepithelioid lymphoma
12464	Peripheral t-cell lymphoma
62437	Malignant reticulosis
58962	Malignant immunoproliferative small intestinal disease
95630	True histiocytic lymphoma
44318	Oth and unspecif peripheral & cutaneous t-cell lymphomas
12335	Malignant lymphoma nos
57427	Malignant lymphoma nos of unspecified site
50696	Malignant lymphoma nos of lymph nodes of head; face and neck
72725	Malignant lymphoma nos of intrathoracic lymph nodes
42579	Malignant lymphoma nos of intra-abdominal lymph nodes
34089	Malignant lymphoma nos of lymph nodes of axilla and arm
63105	Malignant lymphoma nos of lymph node inguinal region and leg
71262	Malignant lymphoma nos of intrapelvic lymph nodes
60092	Malignant lymphoma nos of spleen
15504	Malignant lymphoma nos of lymph nodes of multiple sites
15027	Malignant lymphoma nos
65434	Malignant neoplasms of lymphoid and histiocytic tissue nos
108037	Unspec malig neop lymphoid/histiocytic of unspecified site
64427	Unspec malig neop lymphoid/histiocytic lymph node head/neck
93384	Unspec malig neop lymphoid/histiocytic of intrathoracic node
103353	Unspec malig neop lymphoid/histiocytic intra-abdominal nodes
107638	Unspec malig neop lymphoid/histiocytic lymph node axilla/arm
71609	Unspec malig neop lymphoid/histiocytic nodes inguinal/leg
101465	Unspec malig neop lymphoid/histiocytic of multiple sites
95792	Lymphoid and histiocytic malignancy nos
4944	Multiple myeloma
43552	Kahler's disease
15211	Myelomatosis
22158	Malignant plasma cell neoplasm; extramedullary plasmacytoma
19028	Solitary myeloma
21329	Plasmacytoma nos
46042	Lambda light chain myeloma
39187	Plasma cell leukaemia
19372	Lymphoid leukaemia
4222	Lymphatic leukaemia
4251	Acute lymphoid leukaemia
8625	Chronic lymphoid leukaemia
27790	Chronic lymphatic leukaemia
72774	Subacute lymphoid leukaemia
49725	Other lymphoid leukaemia
31586	Prolymphocytic leukaemia
37461	Adult t-cell leukaemia
38331	Other lymphoid leukaemia nos
38914	Lymphoid leukaemia nos
7176	Myeloid leukaemia
4413	Acute myeloid leukaemia
10726	Chronic myeloid leukaemia
31701	Chronic granulocytic leukaemia
100786	Chronic eosinophilic leukaemia
102783	Chronic neutrophilic leukaemia
27520	Chronic myeloid leukaemia nos
63475	Subacute myeloid leukaemia

70724	Myeloid sarcoma
52327	Chloroma
39629	Granulocytic sarcoma
27664	Acute promyelocytic leukaemia
66089	Other myeloid leukaemia nos
33344	Myeloid leukaemia nos
35875	Monocytic leukaemia
67700	Monoblastic leukaemia
19974	Acute monocytic leukaemia
27458	Chronic monocytic leukaemia
101606	Subacute monocytic leukaemia
99015	Other monocytic leukaemia
103645	Other monocytic leukaemia nos
93342	Monocytic leukaemia nos
37272	Other specified leukaemia
42539	Acute erythraemia and erythroleukaemia
27340	Di guglielmo's disease
37468	Chronic erythraemia
57671	Megakaryocytic leukaemia
65777	Thrombocytic leukaemia
65721	Mast cell leukaemia
50858	Acute panmyelosis
28276	Acute myelofibrosis
94174	Other and unspecified leukaemia
72197	Lymphosarcoma cell leukaemia
99413	Other and unspecified leukaemia nos
30632	Other specified leukaemia nos
25191	Leukaemia of unspecified cell type
4072	Acute leukaemia nos
16416	Chronic leukaemia nos
54793	Subacute leukaemia nos
34692	Other leukaemia of unspecified cell type
4250	Leukaemia nos
20440	Myelomonocytic leukaemia
61500	Acute myelomonocytic leukaemia
22050	Chronic myelomonocytic leukaemia
104475	Subacute myelomonocytic leukaemia
30646	Malignant neoplasm lymphatic or haematopoietic tissue os
49301	Malignant neoplasm lymphatic or haematopoietic tissue nos
50290	Kaposi's sarcoma of lymph nodes
43312	Myeloma - solitary
38321	Plasmacytoma nos
21868	[m]neoplasm, malignant
8627	[m]tumour cells, malignant
22156	[m]malignant tumour, small cell type
24511	[m]malignant tumour, giant cell type
32213	[m]malignant tumour, fusiform cell type
8695	[m]carcinoma nos
16692	[m]carcinomatosis
57336	[m]epithelioma, malignant
25961	[m]large cell carcinoma nos
21609	[m]carcinoma, undifferentiated type, nos
12609	[m]carcinoma, anaplastic type, nos
26413	[m]pleomorphic carcinoma
48048	[m]giant cell and spindle cell carcinoma
35474	[m]giant cell carcinoma

6966	[m]spindle cell carcinoma
54276	[m]pseudosarcomatous carcinoma
69300	[m]polygonal cell carcinoma
61984	[m]spheroidal cell carcinoma
9291	[m]small cell carcinoma nos
66541	[m]round cell carcinoma
9156	[m]oat cell carcinoma
67970	[m]small cell carcinoma, fusiform cell type
30988	[m]small cell carcinoma, intermediate cell
21217	[m]small cell-large cell carcinoma
3028	[m]basal cell carcinoma nos
59919	[m]multicentric basal cell carcinoma
9885	[m]basal cell carcinoma, morphoea type
29524	[m]basal cell carcinoma, fibroepithelial type
35457	[m]basosquamous carcinoma
13574	[m]metatypical carcinoma
2272	[m]adenocarcinomas
8930	[m]adenocarcinoma nos
48223	[m]scirrhous adenocarcinoma
27440	[m]linitis plastica
71895	[m]superficial spreading adenocarcinoma
28272	[m]adenocarcinoma, intestinal type
59240	[m]carcinoma, diffuse type
63102	[m]islet cell carcinoma
95609	[m]insulinoma, malignant
32294	[m]glucagonoma, malignant
98825	[m]mixed islet cell and exocrine adenocarcinoma
49629	[m]gastrinoma, malignant
70516	[m]biliary tract adenomas and adenocarcinomas
98781	[m]trabecular adenocarcinoma
33775	[m]adenoid cystic carcinoma
34879	[m]cylindroid adenocarcinoma
50140	[m]cribriform carcinoma
94083	[m]solid carcinoma nos
34110	[m]carcinoid tumour, malignant
23081	Carcinoid bronchial adenoma
100625	[m]carcinoid tumour, nonargentaffin, malignant
55468	[m]mucocarcinoid tumour, malignant
56794	Adenocarcinoid tumour
26253	[m]neuroendocrine carcinoma
32641	[m]merkel cell carcinoma
10668	[m]renal cell carcinoma
52266	[m]grawitz tumour
15419	[m]hypernephroma
34096	[m]granular cell carcinoma
60775	[m]adrenal cortical carcinoma
16902	[m]basal cell adenocarcinoma
49900	[m]klatskin's tumour
71627	[m]sweat gland adenocarcinoma
28625	[m]mucoepidermoid carcinoma
38442	[m]serous cystadenocarcinoma, nos
65051	[m]papillary cystadenocarcinoma, nos
44930	[m]papillary serous cystadenocarcinoma
95150	[m]serous surface papillary carcinoma
51656	[m]mucinous cystadenocarcinoma nos
66876	[m]pseudomucinous adenocarcinoma

54749	[m]papillary mucinous cystadenocarcinoma
44074	[m]mucin-producing adenocarcinoma
39038	[m]signet ring carcinoma
61588	[m]signet ring cell carcinoma
94438	[m]signet ring carcinoma nos
37688	[m]acinar cell carcinoma
12580	[m]adenosquamous carcinoma
16146	[m]adenocarcinoma with squamous metaplasia
8524	[m]adenoacanthoma
42553	[m]adenocarcinoma with cartilaginous and osseous metaplasia
94810	[m]adenocarcinoma with spindle cell metaplasia
66000	[m]adenocarcinoma with apocrine metaplasia
38770	[m]epithelial-myoepithelial carcinoma
31609	[m]granulosa cell tumour, malignant
29580	[m]sertoli cell carcinoma
95373	[m]leydig cell tumour, malignant
95818	[m]paraganglioma, malignant
65047	[m]phaeochromocytoma, malignant
50605	[m]glomangiosarcoma
105166	[m]glomoid sarcoma
8085	[m]sarcoma nos
31026	[m]spindle cell sarcoma
97463	[m]giant cell sarcoma (except of bone)
46581	[m]pleomorphic cell sarcoma
58837	[m]small cell sarcoma
69844	[m]round cell sarcoma
62396	[m]epithelioid cell sarcoma
28599	[m]liposarcoma nos
101923	[m]fibroliposarcoma
28628	[m]liposarcoma, well differentiated type
56676	[m]myxoid liposarcoma
60127	[m]myxoliposarcoma
103708	[m]round cell liposarcoma
55947	[m]pleomorphic liposarcoma
59651	[m]mixed type liposarcoma
7856	[m]dedifferentiated liposarcoma
31421	[m]rhabdomyosarcoma nos
57505	[m]pleomorphic rhabdomyosarcoma
105944	[m]mixed cell rhabdomyosarcoma
48275	[m]embryonal rhabdomyosarcoma
63247	[m]sarcoma botryoides
42082	[m]alveolar rhabdomyosarcoma
34030	[m]endometrial stromal sarcoma
66607	[m]mixed tumour, malignant, nos
21173	[m]mullerian mixed tumour
21681	Nephroblastoma nos
36870	[m]adenosarcoma
17314	Wilms' tumour
105862	Mesenchymal nephroblastoma
57677	[m]hepatoblastoma
19334	[m]carcinosarcoma nos
67934	[m]carcinosarcoma, embryonal type
61082	Pneumoblastoma
98797	[m]embryonal sarcoma
63518	[m]adenosarcoma
37510	[m]carcinoma in pleomorphic adenoma

17212	[m]rhabdoid sarcoma
18771	[m]clear cell sarcoma of kidney
48348	Pulmonary blastoma
70383	[m]brenner tumour, malignant
59251	[m]cystosarcoma phyllodes, malignant
27509	[m]mesothelioma, malignant
47734	[m]epithelioid mesothelioma, malignant
86820	[m]mesothelioma, biphasic type, malignant
32191	[m]dysgerminoma
7476	[m]seminomas
28941	[m]embryonal carcinoma nos
37621	[m]endodermal sinus tumour
55658	Orchioblastoma
20350	[m]yolk sac tumour
65861	[m]dermoid cyst with malignant transformation
67712	[m]choriocarcinoma
54627	[m]choriocarcinoma combined with teratoma
29945	[m]malignant teratoma, trophoblastic
62348	[m]haemangiosarcoma
22650	[m]angiosarcoma
27439	[m]kaposi's sarcoma
38481	[m]epithelioid haemangioendothelioma, malignant
57729	[m]lymphangiosarcoma
99665	[m]juxtacortical osteogenic sarcoma
63571	[m]parosteal osteosarcoma
105275	[m]periosteal osteogenic sarcoma
7941	[m]chondrosarcoma nos
68220	[m]fibrochondrosarcoma
63659	[m]juxtacortical chondrosarcoma
98559	[m]chondroblastoma, malignant
52684	[m]mesenchymal chondrosarcoma
68956	[m]giant cell tumour of bone, malignant
50859	[m]giant cell bone sarcoma
31673	[m]osteoclastoma, malignant
99797	[m]malignant giant cell tumour of soft parts
4473	[m]ewing's sarcoma
49023	[m]endothelial bone sarcoma
38593	[m]adamantinoma of long bones
67430	[m]tibial adamantinoma
72443	[m]odontogenic tumour, malignant
93175	[m]intraosseous carcinoma
46741	[m]ameloblastic odontosarcoma
97593	[m]ameloblastoma, malignant
100267	[m]adamantinoma, malignant
68730	[m]ameloblastic fibrosarcoma
98483	[m]odontogenic fibrosarcoma
50151	Pineoblastoma
21758	[m]chordoma
31574	[m]glioma, malignant
34252	[m]gliosarcoma
68808	Mixed glioma
39386	Mixed glioma
52751	[m]ependymoma, anaplastic type
46769	[m]ependymoblastoma
27748	Astrocytic glioma
8328	[m]astrocytoma, anaplastic type

45531	Gemistocytic astrocytoma
27846	Fibrillary astrocytoma
30273	Pilocytic astrocytoma
61783	Juvenile astrocytoma
98800	Piloid astrocytoma
103047	Spongioblastoma nos
23083	[m]glioblastoma nos
9575	[m]glioblastoma multiforme
66064	[m]giant cell glioblastoma
27744	Oligodendroglioma nos
49186	[m]oligodendroglioma, anaplastic type
46404	Oligodendroblastoma
34763	[m]medulloblastoma nos
65952	Desmoplastic medulloblastoma
31767	[m]medullomyoblastoma
37473	[m]cerebellar sarcoma nos
41695	[m]primitive neuroectodermal tumour
2123	Neuroblastoma nos
67288	[m]medulloepithelioma nos
107681	[m]teratoid medulloepithelioma
28836	[m]retinoblastomas
51878	[m]aesthesioneuroblastoma
39388	[m]olfactory neuroblastoma
62941	[m]neurofibrosarcoma
69981	[m]neurilemmoma, malignant
37477	[m]schwannoma, malignant
40492	[m]triton tumour, malignant
71869	[m]alveolar soft part sarcoma
17178	[m]lymphomas, nos or diffuse
36114	[m]malignant lymphoma nos
1483	[m]lymphoma nos
23711	[m]malignant lymphoma, diffuse nos
16460	[m]malignant lymphoma, non hodgkin's type
3371	[m]non hodgkins lymphoma
71117	[m]malignant lymphoma, undifferentiated cell type nos
46931	[m]malignant lymphoma, stem cell type
69301	[m]malignant lymphoma, convoluted cell type nos
99655	[m]lymphosarcoma nos
41754	[m]malignant lymphoma, lymphoplasmacytoid type
48253	[m]malignant lymphoma, immunoblastic type
68964	[m]malignant lymphoma, centroblastic-centrocytic, diffuse
41841	[m]malignant lymphoma, follicular centre cell nos
69980	[m]malignant lymphoma, lymphocytic, well differentiated nos
21463	[m]lymphocytic lymphoma nos
60504	[m]lymphocytic lymphosarcoma nos
51852	[m]malig lymphoma, lymphocytic, intermediate different nos
39906	[m]malignant lymphoma, centrocytic
72196	[m]malignant lymphoma, lymphocytic, poorly different nos
67203	[m]lymphoblastic lymphosarcoma nos
34352	[m]lymphoblastic lymphoma nos
52591	Lymphoblastoma nos
72241	[m]prolymphocytic lymphosarcoma
60275	[m]malignant lymphoma, centroblastic type nos
66603	[m]malig lymphoma, follicular centre cell, non-cleaved nos
46877	[m]malignant lymphoma, small lymphocytic nos
31726	[m]malignant lymphoma, small cleaved cell, diffuse

61251	[m]malign lymphoma,lymphocytic,intermediate differn, diffuse
71652	[m]malignant lymphoma, mixed small and large cell, diffuse
58015	[m]malignant lymphomatous polyposis
33869	[m]malignant lymphoma, large cell, diffuse nos
63994	[m]malignant lymphoma, large cell, cleaved, diffuse
71619	[m]malignant lymphoma, large cell, noncleaved, diffuse
51680	[m]malignant lymphoma, small cell, noncleaved, diffuse
51895	[m]lymphoma, diffuse or nos
106137	[m]reticulosarcomas
20710	[m]hodgkin's disease
20437	[m]lymphomas, nodular or follicular
63699	[m]malignant lymphoma, nodular nos
64947	[m]brill - symmers' disease
27562	[m]follicular lymphosarcoma nos
49253	[m]giant follicular lymphoma
98961	[m]malignant lymphoma, centroblastic-centrocytic, follicular
106970	[m]malig lymphoma, lymphocytic, well differentiated,nodular
39883	[m]malig lymp, follicular centre cell, cleaved, follicular
97852	[m]malignant lymphoma, centroblastic type, follicular
58953	[m]malig lymp,follicular centre cell,noncleaved,follicular
40513	[m]lymphoma, nodular or follicular nos
46967	[m]mycosis fungoides
63239	[m]malignant histiocytosis
59593	[m]letterer - siwe disease
45768	[m]acute progressive histiocytosis x
57544	[m]true histiocytic lymphoma
40766	[m] peripheral t-cell lymphoma nos
31492	[m] monocytoid b-cell lymphoma
16774	[m] cutaneous lymphoma
18383	[m] large cell lymphoma
9172	[m]waldenstrom's macroglobulinaemia
31671	[m]plasma cell myeloma
18744	[m]multiple myeloma
3672	[m]myeloma nos
53647	[m]myelomatosis
39490	[m]plasmacytic myeloma
63864	Plasmacytoma nos
102164	[m]monostotic myeloma
73135	[m]solitary myeloma
99702	[m]plasma cell tumour, malignant
94239	[m]mast cell sarcoma
67339	[m]malignant mastocytosis
4637	[m]leukaemias
40420	[m]leukaemias unspecified
41734	[m]leukaemia nos
6316	[m]acute leukaemia nos
22071	[m]blast cell leukaemia
64963	[m]blastic leukaemia
63570	[m]stem cell leukaemia
72179	[m]subacute leukaemia nos
31750	[m]chronic leukaemia nos
72310	[m]aleukaemic leukaemia nos
59929	[m]leukaemia unspecified, nos
48155	[m]lymphoid leukaemias
12146	[m]lymphoid leukaemia nos
20635	[m]lymphatic leukaemia

37410	[m]acute lymphoid leukaemia
41500	[m]chronic lymphoid leukaemia
46048	[m]prolymphocytic leukaemia
50928	[m]burkitt's cell leukaemia
29335	[m]adult t-cell leukaemia/lymphoma
64618	[m]plasma cell leukaemias
46444	[m]erythroleukaemias
70935	[m]erythroleukaemia
100927	[m]erythroleukaemia nos
35697	[m]myeloid leukaemias
71850	[m]myeloid leukaemia nos
37723	[m]granulocytic leukaemia nos
54585	[m]acute myeloid leukaemia
106483	[m]subacute myeloid leukaemia
52942	[m]chronic myeloid leukaemia
66694	[m]naegeli-type monocytic leukaemia
57316	[m]acute promyelocytic leukaemia
46263	[m]acute myelomonocytic leukaemia
48049	[m]chronic myelomonocytic leukaemia
62330	[m]other myeloid leukaemia nos
106197	[m]basophilic leukaemia
57713	[m]eosinophilic leukaemias
71377	[m]eosinophilic leukaemia
107773	[m]eosinophilic leukaemia nos
73088	[m]monocytic leukaemia nos
73066	[m]miscellaneous leukaemias
72222	[m]megakaryocytic leukaemia
69299	[m]thrombocytic leukaemia
93944	[m]chloroma
5915	[m]hairy cell leukaemia
49327	[m]acute megakaryoblastic leukaemia
108316	[m]miscellaneous leukaemia nos
42297	[m]leukaemia nos
31749	[m]monocytoid b-cell lymphoma
27965	[m]angiocentrict-cell lymphoma
58973	[x]malignant neoplasm of lip; oral cavity and pharynx
35180	[x]malignant neoplasm of digestive organs
43490	[x]other specified carcinomas of liver
45766	[x]malignant neoplasm of intestinal tract; part unspecified
49292	[x]malignant neoplsm/ill-defin sites within digestive system
35325	[x]malignant neoplasm of respiratory and intrathoracic orga
40595	[x]malignant neoplasm of bronchus or lung; unspecified
66444	[x]malignant neoplasm/overlap lesion/heart;mediastinm??
99096	[x]malignant neopl/overlapping les/resp???? Organs
86997	[x]malignant neoplasm/ill-defined sites within resp system
50292	[x]malignant neoplasm of mediastinum; part unspecified
40749	[x]malignant neoplasm of bone and articular cartilage
73296	[x]malignant neoplasm/bones??? Cartilage/limb;unspfd
63300	[x]malignant neoplasm/overlap lesion/bone??? Cartilage
43151	[x]malignant neoplasm/bone??? Cartilage; unspecified
19144	[x]melanoma and other malignant neoplasms of skin
56925	[x]malignant melanoma of other???? Parts of face
19444	[x]malignant melanoma of skin; unspecified
57184	[x]oth malignant neoplasm/skin of oth??? Parts of face
56121	[x]malignant neoplasm of skin; unspecified
40592	[x]malignant neoplasm of mesothelial and soft tissue

67034	[x]mesothelioma of other sites
21715	[x]mesothelioma of lung
30526	[x]mesothelioma; unspecified
93665	[x]kaposi's sarcoma; unspecified
101668	[x]malignant neoplasm/peripheral nerves of trunk;unspecified
105072	[x]mal neoplasm/overlap les/periph nerv??? Nerv systm
95671	[x]malignant neoplasm of peritoneum; unspecified
91896	[x]mal neoplasm/connective? Tissue of trunk;unspecified
91457	[x]malignant neoplasm/connective soft tissue;unspecified
60162	[x]malignant neoplasm overlapping lesion of skin
12499	[x]malignant neoplasm of breast
40598	[x]malignant neoplasm of female genital organs
64497	[x]malignant neoplasm of uterine adnexa; unspecified
57756	[x]malignant neoplasm/other specified female genital organs
55588	[x]malignant neoplasm of female genital organ; unspecified
40671	[x]malignant neoplasm of male genital organs
57191	[x]malignant neoplasm/other specified male genital organs
45262	[x]malignant neoplasm of male genital organ; unspecified
35113	[x]malignant neoplasm of urinary tract
45260	[x]malignant neoplasm of urinary organ; unspecified
35285	[x]malignant neoplasm of eye; brain and other parts of cent
68027	[x]malignant neoplasm/other and unspecified cranial nerves
41515	[x]malignant neoplasm/central nervous system; unspecified
63925	[x]malignant neoplasm of meninges; unspecified
47633	[x]malig neopl; overlap lesion brain & other part of cns
39027	[x]malignant neoplasm of other specified sites
40740	[x]malignant neoplasms of lymphoid; haematopoietic and rela
43415	[x]other hodgkin's disease
67518	[x]other types of follicular non-hodgkin's lymphoma
98596	[x]other types of diffuse non-hodgkin's lymphoma
64336	[x]other specified types of non-hodgkin's lymphoma
102688	[x]other malignant immunoproliferative diseases
67029	[x]other lymphoid leukaemia
61693	[x]other myeloid leukaemia
89762	[x]other monocytic leukaemia
89329	[x]other specified leukaemias
65165	[x]other leukaemia of unspecified cell type
105025	[x]oth spcf mal neoplsm/lymphoid;haematopoietic? Tissue
72500	[x]mal neoplasm/lymphoid,haematopoietic+related tissu,unspcf
64515	[x]diffuse non-hodgkin's lymphoma; unspecified
63375	[x]unspecified b-cell non-hodgkin's lymphoma
8649	[x]non-hodgkin's lymphoma; unspecified type
7940	[x]non-hodgkin's lymphoma nos
63598	[x]malignant neoplasms/independent (primary) multiple sites
64897	[x]malignant neoplasms/independent(primary)multiple sites
10335	Cancer confirmed
32351	Squamous cell carcinoma antigen level
52946	Bone marrow: myeloma cells
10178	Gleason grading of prostate cancer
18503	Gleason prostate grade 2-4 (low)
18612	Gleason prostate grade 5-7 (medium)
26081	Gleason prostate grade 8-10 (high)
37793	Figo staging of gynaecological malignancy
104609	Clark melanoma level 2
102116	Clark melanoma level 4
30283	Intravesical install chemotherapeutic agent for malignancy

18270	Excision malignant skin tumour
11834	Excision biopsy of rodent ulcer
93402	Excision biopsy of basal cell carcinoma
26197	Administration of cancer treatment
32411	Cancer treatment started
54336	Cancer hospital treatment completed
10292	Cancer diagnosis discussed
11075	Cancer diagnosis discussed with significant other
22382	Cancer diagnosis discussed with patient
44952	Date cancer diagnosis received in primary care
26076	Cancer pain and symptom management
59054	Cancer rehabilitation and readaption
94000	Bowel cancer detected by national screening programme
67575	Hiv disease resulting in unspecified malignant neoplasm
27853	Hiv disease resulting in kaposi's sarcoma
108054	Hiv disease resulting in kaposi sarcoma
105324	Hiv disease resulting in multiple malignant neoplasms
51708	Hiv dis reslt/oth mal neopl/lymph,h'matopoetc+reltd tissu
98142	Siewert type i adenocarcinoma
97499	Siewert type ii adenocarcinoma
96094	Siewert type iii adenocarcinoma
101700	Hereditary nonpolyposis colon cancer
96445	Malignant neoplasm of turbinate
92382	Malignant neoplasm of fourth metatarsal bone
876	Basal cell carcinoma
1940	Rodent ulcer
3445	Epithelioma basal cell
93352	Squamous cell carcinoma of skin
93490	Squamous cell carcinoma of skin nos
105488	Local recurrence of malignant tumour of breast
91509	Malignant neoplasm of descended testis nos
105388	Local recurrence of malignant tumour of urinary bladder
100083	Neuroblastoma
26034	Other malignant neoplasm nos
51352	Malignant neoplasms of independent (primary) multiple sites
11035	Primary malignant neoplasm of unknown site
104324	Malignant tumour of unknown origin
54267	Malignant neoplasm of unspecified site nos
104291	Hodgkin lymphoma
104895	Nodular lymphocyte predominant hodgkin lymphoma
105841	Nodular sclerosis classical hodgkin lymphoma
106597	Lymphocyte-rich classical hodgkin lymphoma
104484	Other classical hodgkin lymphoma
106349	Hodgkin lymphoma nos
87335	Hairy cell leukaemia
104391	Non-hodgkin lymphoma
95715	Mucosa-associated lymphoma
101114	Diffuse non-hodgkin's large cell lymphoma
102594	Diffuse large b-cell lymphoma
105966	Extranod marg zone b-cell lymphom mucosa-assoc lymphoid tiss
105038	Mediastinal (thymic) large b-cell lymphoma
104152	Follicular lymphoma
105889	Follicular lymphoma grade 1
105095	Follicular lymphoma grade 2
107166	Follicular lymphoma grade 3
105020	Follicular lymphoma grade 3a

107973	Follicular lymphoma grade 3b
106969	Diffuse follicle centre lymphoma
106063	Other types of follicular lymphoma
105335	Sarcoma of dendritic cells
105762	Unifocal langerhans-cell histiocytosis
105083	Histiocytic sarcoma
105085	T/nk-cell lymphoma
105559	Anaplastic large cell lymphoma, alk-positive
105955	Anaplastic large cell lymphoma, alk-negative
104862	Cutaneous t-cell lymphoma
107949	Hepatosplenic t-cell lymphoma
105709	Enteropathy-associated t-cell lymphoma
105925	Subcutaneous panniculitic t-cell lymphoma
105375	Blastic nk-cell lymphoma
105636	Angioimmunoblastic t-cell lymphoma
104934	Other mature t/nk-cell lymphoma
106884	Nonfollicular lymphoma
106867	Non-follicular lymphoma
104386	Small cell b-cell lymphoma
104620	Mantle cell lymphoma
104412	Lymphoblastic (diffuse) lymphoma
104418	Solitary plasmacytoma
104325	B-cell acute lymphoblastic leukaemia
104328	B-cell chronic lymphocytic leukaemia
107017	Chronic lymphocytic leukaemia of b-cell type
107052	Clinical stage a chronic lymphocytic leukaemia
106924	Clinical stage b chronic lymphocytic leukaemia
107163	Clinical stage c chronic lymphocytic leukaemia
107643	T-cell prolymphocytic leukaemia
104939	Adult t-cell lymphoma/leukaemia (htlv-1-associated)
105957	Chronic myeloid leukaemia, bcr/abl positive
107236	Atypical chronic myeloid leukaemia, bcr/abl negative
104788	Acute myeloblastic leukaemia
108424	Acute monoblastic leukaemia
104273	Myelodysplastic and myeloproliferative disease
105069	Juvenile myelomonocytic leukaemia
104684	Multiple self-healing epithelioma of ferguson-smith
5136	Choriocarcinoma
50569	Neo/uncertn+unknwn behav/lymph,h'matopetc+rel tiss,unspcf
22267	[m]neoplasm, malig, uncertain whether primary or metastatic
10541	[m]papillary carcinoma nos
34395	[m]verrucous carcinoma nos
43717	[m]verrucous epidermoid carcinoma
4852	[m]verrucous squamous cell carcinoma
20807	[m]papillary squamous cell carcinoma
67912	[m]papillary epidermoid carcinoma
1624	[m]squamous cell carcinoma nos
56600	[m]epidermoid carcinoma nos
57680	[m]spinous cell carcinoma
94873	[m]squamous cell carcinoma of skin nos
29787	[m]squamous cell carcinoma, keratinising type nos
57513	[m]epidermoid carcinoma, keratinising type
59143	[m]squamous cell carcinoma, large cell, non-keratinising
41816	[m]squamous cell carcinoma, small cell, non-keratinising
45458	[m]squamous cell carcinoma, spindle cell type
31004	[m]adenoid squamous cell carcinoma

33497	[m]squamous cell carcinoma, microinvasive
45510	[m]lymphoepithelial carcinoma
102417	[m]superficial basal cell carcinoma
102547	[m]basal cell carcinoma, nodular
103440	[m]basal cell carcinoma, micronodular
103178	[m]basal cell carcinoma, infiltrative
103066	[m]pigmented basal cell carcinoma
6436	[m]transitional cell carcinoma nos
12388	[m]urothelial carcinoma
100111	[m]schneiderian carcinoma
58798	[m]transitional cell carcinoma, spindle cell type
38454	[m]basaloid carcinoma
65216	[m]cloacogenic carcinoma
9712	[m]papillary transitional cell carcinoma
101095	[m]grade 1 (stage pta) papillary urothelial/transit cell ca
102244	[m]grade 2 (stage pta) papillary urothelial/transit cell ca
101978	[m]grade 3 (stage pta) papillary urothelial/transit cell ca
44778	[m]adenocarcinoma in tubulovillous adenoma
8711	[m]cholangiocarcinoma
40438	[m]bile duct carcinoma
41313	[m]bile duct cystadenocarcinoma
40240	[m]hepatocellular carcinoma nos
26814	[m]hepatoma, malignant
25641	[m]liver cell carcinoma
107299	[m]combined hepatocellular carcinoma and cholangiocarcinoma
46771	[m]hepatocellular carcinoma, fibrolamellar
60756	[m]cylindroid bronchial adenoma
52326	[m]adenocarcinoma in adenomatous polyp
73434	[m]adenocarcinoma in multiple adenomatous polyps
60045	[m]tubular adenocarcinoma
73275	[m]adenocarcinoma in adenomatous polposis coli
69210	[m]goblet cell tumour
34015	[m]bronchiolo-alveolar adenocarcinoma
36530	[m]alveolar cell carcinoma
16723	[m]bronchiolar carcinoma
57802	[m]alveolar adenocarcinoma
35348	[m]papillary adenocarcinoma nos
67342	[m]adenocarcinoma in villous adenoma
27849	[m]villous adenocarcinoma
68456	[m]chromophobe carcinoma
36876	[m]eosinophil carcinoma
72277	[m]basophil carcinoma
40622	[m]mucoid cell carcinoma
71497	[m]oxyphilic adenocarcinoma
29008	[m]hurthle cell adenocarcinoma
53129	[m]oncytic adenocarcinoma
37354	[m]clear cell adenocarcinoma nos
21741	[m]follicular adenocarcinoma nos
21847	[m]follicular carcinoma
59918	[m]follicular adenocarcinoma, well differentiated type
61467	[m]follicular adenocarcinoma, trabecular type
46761	[m]papillary and follicular adenocarcinoma
68757	[m]nonencapsulated sclerosing carcinoma
9447	[m]endometrioid carcinoma
103034	[m]endometrioid adenofibroma, malignant
61764	[m]vipoma

68783	[m]skin appendage carcinoma
38575	[m]apocrine adenocarcinoma
34269	[m]sebaceous adenocarcinoma
34000	[m]cystadenocarcinoma nos
69978	[m]borderline mucinous cystadenoma of the ovary
52263	[m]serous cystadenoma, borderline malignancy
98696	[m]papillary cystadenoma, borderline malignancy
28396	[m]mucinous cystadenoma, borderline malignancy
21131	[m]serous cystadenoma, borderline malignancy
46113	[m]papillary cystadenoma, borderline malignancy
6203	[m]papillary serous cystadenoma, borderline malignancy
12497	[m]mucinous adenocarcinoma
30416	[m]colloid adenocarcinoma
95008	[m]gelatinous adenocarcinoma
55429	[m]mucoid adenocarcionoma
59284	[m]mucous adenocarcinoma
8351	[m]infiltrating duct carcinoma
21833	[m]duct carcinoma nos
30189	[m]intraductal papillary adenocarcinoma with invasion
39760	[m]infiltrating duct and lobular carcinoma
58131	[m]comedocarcinoma nos
40359	[m]juvenile breast carcinoma
67701	[m]secretory breast carcinoma
16677	[m]medullary carcinoma nos
47920	[m]c cell carcinoma
50946	[m]medullary carcinoma with amyloid stroma
98883	[m]medullary carcinoma with lymphoid stroma
12427	[m]lobular carcinoma nos
7319	[m]infiltrating ductular carcinoma
32472	[m]inflammatory carcinoma
12300	[m]paget's disease, mammary
60803	[m]paget's disease, breast
42542	[m]paget's disease and infiltrating breast duct carcinoma
12480	[m]paget's disease and intraductal carcinoma of breast
24523	[m]paget's disease, extramammary, exc paget's disease bone
3969	[m]intracystic carcinoma nos
59415	[m]thymoma, malignant
579	[m]malignant melanoma nos
24551	[m]melanocarcinoma
44157	[m]melanosarcoma nos
67966	[m]naevocarcinoma
51353	[m]malignant melanoma, regressing
58835	[m]desmoplastic melanoma, malignant
20982	[m]nodular melanoma
68889	[m]balloon cell melanoma
17232	[m]amelanotic melanoma
63574	[m]malignant melanoma in junctional naevus
62088	[m]malignant melanoma in hutchinson's melanotic freckle
11922	[m]lentigo maligna melanoma
22692	[m]acral lentiginous melanoma, malignant
24208	[m]superficial spreading melanoma
73251	[m]malignant melanoma in giant pigmented naevus
23085	[m]epithelioid cell melanoma
44061	[m]spindle cell melanoma nos
92293	[m]spindle cell melanoma, type b
40303	[m]mixed epithelioid and spindle melanoma

68447	[m]blue naevus, malignant
31323	[m]fibrosarcoma nos
8088	[m]fibromyxosarcoma
95024	[m]infantile fibrosarcoma
94286	[m]congenital fibrosarcoma
37680	[m]fibrous histiocytoma, malignant
96231	[m]fibroxanthoma, malignant
35034	[m]fibroxanthosarcoma
26881	[m]dermatofibroma protuberans
31772	[m]dermatofibrosarcoma nos
31090	[m]pigmented dermatofibrosarcoma protuberans
21732	[m]myxosarcoma
10588	[m]leiomyosarcoma nos
73916	[m]epithelioid leiomyosarcoma
64596	[m]myxoid leiomyosarcoma
67019	[m]angiomyosarcoma
55268	[m]myosarcoma
49811	[m]mesodermal mixed tumour
106889	[m]embryonal hepatoma
87003	[m]mesenchymoma, malignant
50379	[m]synovial sarcoma nos
105073	[m]synovial sarcoma, spindle cell type
57796	[m]synovial sarcoma, biphasic type
63286	[m]clear cell sarcoma of tendons and aponeuroses
104720	[m]sarcomatoid mesothelioma
21770	[m]mesothelioma, unspecified
57084	[m]seminoma, anaplastic type
35223	[m]spermatocytic seminoma
9859	[m]seminoma nos
27971	[m]germinoma
102356	[m]polyembryoma
33636	[m]teratoma, malignant, nos
57087	[m]embryonal teratoma
43865	[m]immature teratoma
52493	[m]teratoblastoma, malignant
37542	[m]teratocarcinoma
61542	[m]malignant teratoma, undifferentiated type
21682	[m]malignant teratoma, intermediate type
71301	[m]struma ovarii, malignant
35071	[m]mixed germ cell tumour
98322	[m]haemangioendothelioma, malignant
105296	[m]haemangiopericytoma, malignant
8660	[m]osteosarcoma nos
49862	[m]osteoblastic sarcoma
59310	[m]osteochondrosarcoma
5052	[m]osteogenic sarcoma nos
24539	[m]chondroblastic osteosarcoma
21447	[m]fibroblastic osteosarcoma
22561	[m]telangiectatic osteosarcoma
60631	[m]osteosarcoma in paget's disease of bone
4118	[m]myxoid chondrosarcoma
29337	[m] small cell osteosarcoma
12309	[m]gliomas
8523	[m]glioma nos
38551	[m]gliomatosis cerebri
20084	[m]ependymoma nos

8547	[m]astrocytoma nos
50235	[m]astroblastoma
67587	[m]pleomorphic xanthoastrocytoma
107884	[m]peripheral neuroectodermal tumour
27653	[m]glioma nos
54284	[m]neuroepitheliomatous neoplasms
39121	[m]ganglioneuroblastoma
97961	[m]neuroepithelioma nos
103883	[m]retinoblastoma, undifferentiated type
48952	[m]retinoblastoma nos
58902	[m]olfactory neurogenic tumour
106131	[m]olfactory neuroepithelioma
99491	[m]neuroepitheliomatous neoplasm nos
27363	[m]meningioma, malignant
60347	[m]leptomeningeal sarcoma
96798	[m]meningothelial sarcoma
106134	[m]meningeal sarcomatosis
72433	[m]reticulosarcoma nos
49825	[m]reticulum cell sarcoma nos
100544	[m]reticulosarcoma, nodular
61997	[m]hodgkin's disease nos
101429	[m]lymphogranuloma, malignant
56041	[m]hodgkin's disease, lymphocytic predominance
65584	[m]hodgkin,s disease, lymphocytic predominance, diffuse
31537	[m]hodgkin,s disease, lymphocytic predominance, nodular
51285	[m]hodgkin's disease, mixed cellularity
96183	[m]hodgkin's disease,lymphocytic depletion,diffuse fibrosis
42198	[m]hodgkin's disease, nodular sclerosis nos
40508	[m]hodgkin,s disease, nodular sclerosis, lymphocytic predom
64343	[m]hodgkin,s disease, nodular sclerosis, mixed cellularity
31741	[m]hodgkin,s disease, nodular sclerosis, lymphocytic deplet
99200	[m]hodgkin's disease, nodular sclerosis, cellular phase
89230	[m]hodgkin's granuloma
42769	[m]hodgkin's disease nos
95464	[m]mycosis fungoides
97756	[m]sezary's disease
99695	[m]mycosis fungoides nos
63973	[m]microglioma
70740	[m]malignant reticulosis
47330	[m]histiocytic medullary reticulosis
26135	[m] alpha heavy chain disease
52593	[m] gamma heavy chain disease
68353	[m] angioendotheliomatosis
24317	[m]myelosis nos
96893	[m]myeloid sarcoma
98009	[m]granulocytic sarcoma
102764	[m]acute panmyelosis
37487	[m]acute myelofibrosis
101271	[m]acute panmyelosis
107281	[m]neuroendocrine neoplasm
98361	[x]kaposi's sarcoma of other sites
40608	[x]malignant neoplasm of thyroid and other endocrine glands
64309	[x]malignant neoplasm of endocrine gland, unspecified
96226	[x]malignant neoplasm/overlap lesion/other+ill-defined sites
52029	[x]malignant neoplasm without specification of site
107587	Multiple endocrine neoplasia syndrome type 1

10411	Waldenstrom's macroglobulinaemia
108235	Waldenstrom macroglobulinaemia
101350	Alpha heavy chain disease
99067	Gamma heavy chain disease
48145	Anaemia in ovarian carcinoma
30537	Polyneuropathy in malignant disease
57551	Myasthenic syndrome due to other malignancy
49482	Myopathy due to malignant disease
60433	Osteoporosis in multiple myelomatosis
5069	Meckel's diverticulum
33781	Meckel's diverticulum nos
51029	Mast cell disease
17521	Mastocytosis
31561	[v]follow-up examination aft surgery for malignant neoplasm
42509	[v]follow-up exam aft combined treatment for malig neoplasm
44421	[v]folow-up exam aft other treatment for malignant neoplasm
36321	[v]folow-up exam aft unspec treatment for malignant neoplasm

Moderate or severe renal disease

Medcode	Description
103532	[X]Heredtry nephrpthy NEC difus mesangiocapilry glomneph
56893	Chron neph syn difus mesangial prolifrtiv glomerulonephritis
57168	Chron nephritic syndrom difuse membranous glomerulonephritis
65400	Chronic diffuse glomerulonephritis
4669	Chronic focal glomerulonephritis
97758	Chronic glomerulonephritis diseases EC
15097	Chronic glomerulonephritis NOS
29013	Chronic kidney disease stage 1
12586	Chronic kidney disease stage 2
12566	Chronic kidney disease stage 3
12479	Chronic kidney disease stage 4
12585	Chronic kidney disease stage 5
61494	Chronic membranoproliferative glomerulonephritis
10809	Chronic membranous glomerulonephritis
73026	Chronic neph syn difus mesangiocapillary glomerulonephritis
60857	Chronic nephritic syn diffuse crescentic glomerulonephritis
57568	Chronic pyelonephritis with medullary necrosis
99631	Chronic pyelonephritis without medullary necrosis
65064	Chronic rapidly progressive glomerulonephritis
67995	Focal membranoproliferative glomerulonephritis
8828	H/O: nephritis
41881	Mesangiocapillary glomerulonephritis NEC
36342	Mesangioproliferative glomerulonephritis NEC
67193	Nephritis unsp membranoprolif glomerulonephritis lesion
94350	Nephritis unsp????? glomerulonephritis lesion NOS
2773	Nephritis; nephrosis and nephrotic syndrome
21989	Nephrotic syn;diffuse mesangiocapillary glomerulonephritis
99644	Nephrotic syndrome??????? glomerulonephritis
63615	Other chronic glomerulonephritis NOS
34648	Renal dwarfism
50728	Renal infantilism
66062	Renal rickets
53940	[X]Other chronic renal failure

61930	[X]Renal failure
7804	Chronic glomerulonephritis
512	Chronic renal failure
6712	End stage renal failure
56939	Hypokalaemic nephropathy
6842	Impaired renal function
25980	Impaired renal function disorder NOS
12465	Membranoproliferative nephritis unspecified
10647	Nephritis - chronic
4850	Nephritis and nephropathy unspecified
33580	Nephritis and nephropathy unspecified
30310	Nephrogenic diabetes insipidus
11875	Nephropathy - chronic
50804	Other impaired renal function disorder NOS
68114	Phosphate-losing tubular disorders
41676	Renal cortical necrosis unspecified
350	Renal failure unspecified
45867	Renal medullary necrosis unspecified
29638	Renal osteodystrophy
34637	Renal osteodystrophy NOS
101453	[X]Other chronic tubulo-interstitial nephritis
96819	[X]Other disorders resulting/impaired renal tubular function
94842	[X]Renal tubulo-interstitial diseases
100693	[X]Renal tubulo-interstitial disorders/transplant rejection
63000	Benign hypertensive heart and renal disease
10081	Chronic uraemia
64636	Compensation for renal failure NOS
11773	Dialysis for renal failure
24736	Drug/heavy-metal-induced tubulo-interstitial and tub conditn
53852	End stage renal failure
8330	End-stage renal disease
112094	Failed attempted abortion with renal failure
8668	Glomerular disease
7190	Glomerulosclerosis
2996	Haemodialysis NEC
57987	Hyperten heart&renal dis+both(congestv)heart and renal fail
63466	Hypertensive heart and renal disease
68659	Hypertensive heart and renal disease NOS
28684	Hypertensive heart and renal disease with renal failure
21837	Hypertensive heart&renal dis wth (congestive) heart failure
4668	Hypertensive renal disease
32423	Hypertensive renal disease with renal failure
8919	Impaired renal function disorder
8037	Insertion of ambulatory peritoneal dialysis catheter
30709	Insertion of temporary peritoneal dialysis catheter
28158	Kidney dialysis with complication, without blame
39598	Kidney failure as a complication of care
54990	Kidney transplant with complication, without blame
67232	Malignant hypertensive heart and renal disease
39649	Malignant hypertensive renal disease
5291	Membranous nephritis unspecified
31402	Necrotising renal papillitis
15780	Nephritis, nephrosis and nephrotic syndrome NOS
11873	Nephropathy, unspecified
2999	Nephrotic syndrome
35065	Other nephritis and nephrosis unspecified

48022	Other specified compensation for renal failure
49150	Other specified nephritis, nephrosis or nephrotic syndrome
2994	Peritoneal dialysis
59194	Placement ambulatory apparatus- compensate renal failure OS
56760	Placement ambulatory apparatus compensation renal failure
36442	Placement ambulatory dialysis apparatus - compens renal fail
65089	Placement other apparatus- compensate for renal failure NOS
107901	Placement other apparatus- compensate for renal failure OS
83513	Placement other apparatus for compensation for renal failure
23960	Potter's syndrome
16008	Proliferative nephritis unspecified
58164	Rapidly progressive nephritis unspecified
67261	Ren tub-interstitl disordr/systemc connectv tiss disorder
20073	Renal dialysis
66714	Renal dialysis with complication, without blame
63760	Renal failure after crushing
11554	Renal failure as a complication of care
41013	Renal function impairment with growth failure
11787	Renal impairment
18774	Renal transplant with complication, without blame
41148	Renal tubulo-interstitial disorder in SLE
64622	Renal tubulo-interstitial disorder/ neoplastic diseases
45523	Renal tubulo-interstitial disorders in diseases EC
48057	Renal tubulo-interstitial disordrs in transplant rejectn
20516	Salt-losing nephritis
101756	Thomas intravascular shunt for dialysis
62520	Unsp nephrit synd, diff endocap prolif glomerulonephritis
30301	Unsp nephrit synd, diff mesang prolif glomerulonephritis
36125	Unspecif nephr synd, diff concentric glomerulonephritis
101666	Unspecified abortion with renal failure
5182	Unspecified glomerulonephritis NOS
60128	Unspecified nephritic syndrome, dense deposit disease
4809	Uraemia NOS

Metastasis

Medcode	Description
97091	[X]2ndry malignant neoplasm/bladder??? urinary organs
68332	[X]2ndry malignant neoplasm/oth?? parts/nervous system
66163	[X]2ndry?? malignant neoplasm lymph nodes/multi regions
6170	Carcinomatosis
13569	Disseminated malignancy NOS
65466	Kaposi's sarcoma of multiple organs
35186	[X]Malignant neoplasm of ill-defined; secondary and unspeci
54253	[X]Secondary malignant neoplasm of other specified sites
57481	[X]Secondary malignant neoplasm/oth? respiratory organs
88022	[X]Secondary malignant neoplasm/oth?? digestive organs
5199	Cerebral metastasis
4403	Liver metastases
7830	Lymph node metastases
6471	Metastases of respiratory and/or digestive systems
18676	Pathological fracture due to metastatic bone disease
25366	Secondary and unspec malig neop ant mediastinal lymph nodes
44627	Secondary and unspec malig neop anterior cervical LN

50199	Secondary and unspec malig neop axilla and upper limb LN
73538	Secondary and unspec malig neop axilla and upper limb LN NOS
37540	Secondary and unspec malig neop axillary lymph nodes
62124	Secondary and unspec malig neop bronchopulmonary lymph nodes
101662	Secondary and unspec malig neop circumflex iliac LN
41691	Secondary and unspec malig neop coeliac lymph nodes
18658	Secondary and unspec malig neop common iliac lymph nodes
68611	Secondary and unspec malig neop deep cervical LN
61289	Secondary and unspec malig neop deep inguinal lymph nodes
92703	Secondary and unspec malig neop deep parotid lymph nodes
95378	Secondary and unspec malig neop diaphragmatic lymph nodes
69132	Secondary and unspec malig neop external iliac lymph nodes
61677	Secondary and unspec malig neop inferior mesenteric LN
69392	Secondary and unspec malig neop inferior tracheobronchial LN
50904	Secondary and unspec malig neop infraclavicular lymph nodes
63915	Secondary and unspec malig neop inguinal and lower limb LN
105953	Secondary and unspec malig neop intercostal lymph nodes
84368	Secondary and unspec malig neop internal iliac lymph nodes
37919	Secondary and unspec malig neop internal mammary lymph nodes
44931	Secondary and unspec malig neop intra-abdominal LN NOS
52736	Secondary and unspec malig neop intra-abdominal lymph nodes
72803	Secondary and unspec malig neop intrapelvic LN NOS
6701	Secondary and unspec malig neop intrapelvic lymph nodes
93716	Secondary and unspec malig neop intrathoracic LN NOS
64116	Secondary and unspec malig neop intrathoracic lymph nodes
49214	Secondary and unspec malig neop lymph nodes head/face/neck
20159	Secondary and unspec malig neop lymph nodes multiple sites
15507	Secondary and unspec malig neop lymph nodes NOS
28059	Secondary and unspec malig neop of facial lymph nodes
70747	Secondary and unspec malig neop of inguinal and leg LN NOS
64918	Secondary and unspec malig neop of superficial parotid LN
58692	Secondary and unspec malig neop paratracheal lymph nodes
46409	Secondary and unspec malig neop pectoral lymph nodes
55463	Secondary and unspec malig neop post mediastinal lymph nodes
52190	Secondary and unspec malig neop pulmonary lymph nodes
47366	Secondary and unspec malig neop sacral lymph nodes
39433	Secondary and unspec malig neop submandibular lymph nodes
38343	Secondary and unspec malig neop submental lymph nodes
67797	Secondary and unspec malig neop superfic tracheobronchial LN
33395	Secondary and unspec malig neop superficial cervical LN
54278	Secondary and unspec malig neop superficial inguinal LN
72713	Secondary and unspec malig neop superficial mesenteric LN
98626	Secondary and unspec malig neop supratrochlear lymph nodes
66775	Secondary and unspec malignant neoplasm mastoid lymph nodes
65253	Secondary and unspec malignant neoplasm occipital lymph node
9618	Secondary and unspecified malignant neoplasm of lymph nodes
97832	Secondary cancer of the cervix
65490	Secondary cancer of the vulva
27651	Secondary carcinoma of other specified sites
24301	Secondary carcinoma of respiratory and/or digestive systems
36200	Secondary malig neop of large intestine or rectum NOS
35053	Secondary malig neop of respiratory and digestive systems
66083	Secondary malig neop of respiratory or digestive system NOS
67396	Secondary malig neop of retroperitoneum and peritoneum
97672	Secondary malig neop of retroperitoneum or peritoneum NOS
70026	Secondary malig neop of small intestine or duodenum NOS

36401	Secondary malignant neoplasm of adrenal gland
22146	Secondary malignant neoplasm of bladder
7654	Secondary malignant neoplasm of bone and bone marrow
5198	Secondary malignant neoplasm of brain
33843	Secondary malignant neoplasm of brain and spinal cord
59375	Secondary malignant neoplasm of brain or spinal cord NOS
16760	Secondary malignant neoplasm of breast
73616	Secondary malignant neoplasm of cervix uteri
28727	Secondary malignant neoplasm of colon
55946	Secondary malignant neoplasm of duodenum
104480	Secondary malignant neoplasm of epididymis and vas deferens
99511	Secondary malignant neoplasm of ileum
110433	Secondary malignant neoplasm of jejunum
1952	Secondary malignant neoplasm of kidney
44529	Secondary malignant neoplasm of large intestine and rectum
36147	Secondary malignant neoplasm of liver
15103	Secondary malignant neoplasm of liver
4137	Secondary malignant neoplasm of lung
51551	Secondary malignant neoplasm of mediastinum
56345	Secondary malignant neoplasm of other digestive organ
54120	Secondary malignant neoplasm of other part of nervous system
62584	Secondary malignant neoplasm of other respiratory organs
22524	Secondary malignant neoplasm of other specified site NOS
16500	Secondary malignant neoplasm of other specified site NOS
5842	Secondary malignant neoplasm of other specified sites
18616	Secondary malignant neoplasm of other specified sites
62828	Secondary malignant neoplasm of other urinary organ NOS
73213	Secondary malignant neoplasm of other urinary organs
44615	Secondary malignant neoplasm of ovary
49145	Secondary malignant neoplasm of penis
27391	Secondary malignant neoplasm of peritoneum
16213	Secondary malignant neoplasm of pleura
21590	Secondary malignant neoplasm of prostate
62909	Secondary malignant neoplasm of rectum
35364	Secondary malignant neoplasm of retroperitoneum
19945	Secondary malignant neoplasm of skin
55096	Secondary malignant neoplasm of skin NOS
9505	Secondary malignant neoplasm of skin of breast
100296	Secondary malignant neoplasm of skin of face
43930	Secondary malignant neoplasm of skin of head
48828	Secondary malignant neoplasm of skin of hip and leg
35999	Secondary malignant neoplasm of skin of neck
63896	Secondary malignant neoplasm of skin of shoulder and arm
41144	Secondary malignant neoplasm of skin of trunk
64680	Secondary malignant neoplasm of small intestine and duodenum
38918	Secondary malignant neoplasm of spinal cord
34145	Secondary malignant neoplasm of testis
45824	Secondary malignant neoplasm of tongue
54679	Secondary malignant neoplasm of unknown site
60134	Secondary malignant neoplasm of ureter
53528	Secondary malignant neoplasm of urethra
55090	Secondary malignant neoplasm of uterus
70736	Secondary malignant neoplasm of vagina
60335	Secondary malignant neoplasm of vulva
67129	Secondary unspec malig neop lymph nodes head/face/neck NOS
5455	[M]Adenocarcinoma, metastatic, NOS

3152	[M]Carcinoma, metastatic, NOS
54874	[M]Metastatic signet ring cell carcinoma
22267	[M]Neoplasm, malig, uncertain whether primary or metastatic
3197	[M]Neoplasm, metastatic
9366	[M]Secondary carcinoma
6985	[M]Secondary neoplasm
24293	[M]Squamous cell carcinoma, metastatic NOS
8600	Pain from metastases
112718	secondary malignant neoplasm of liver intrahepatic bile duct
101836	human immunodeficiency virus with secondary cancers

AIDS

Medcode	Description
44288	[D]Laboratory evidence of human immunodefiency virus [HIV]
41185	[X]Dementia in human immunodef virus [HIV] disease
112034	[X]HIV dis reslt/oth mal neopl/lymph;h'matopoetc? tissu
96751	[X]HIV disease result/haematological???? abnorms;NEC
112037	[X]HIV disease resulting in multiple diseases CE
102117	[X]HIV disease resulting in multiple infections
112030	[X]HIV disease resulting in other bacterial infections
112035	[X]HIV disease resulting in other malignant neoplasms
112031	[X]HIV disease resulting in other mycoses
112033	[x]hiv disease resulting in other non-hodgkin lymphoma
69767	[X]HIV disease resulting in other non-Hodgkin's lymphoma
102252	[X]HIV disease resulting in other specified conditions
107807	[X]HIV disease resulting in other viral infections
112036	[X]HIV disease resulting in unspecified malignant neoplasm
104134	[X]HIV disease resulting/other infectious??? diseases
112032	[X]HIV disease resulting/unspcf infectious??? disease
62854	[X]Human immunodeficiency virus disease
100769	[X]Unspecified human immunodeficiency virus [HIV] disease
36294	Acquired human immunodeficiency virus infection syndrome NOS
23770	Acquired immune deficiency syndrome
58857	Acute human immunodeficiency virus infection
23763	AIDS carrier
58859	Asymptomatic human immunodeficiency virus infection
51708	HIV dis reslt/oth mal neopl/lymph;h'matopoetc? tissu
66367	HIV dis resulting oth types of non-Hodgkin's lymphoma
104466	hiv disease complicating pregnancy childbirth puerperium
47632	HIV disease result/haematological???? abnorms;NEC
111980	hiv disease resulting in burkitt lymphoma
44617	HIV disease resulting in Burkitt's lymphoma
23951	HIV disease resulting in candidiasis
66368	HIV disease resulting in cytomegaloviral disease
108054	hiv disease resulting in kaposi sarcoma
27853	HIV disease resulting in Kaposi's sarcoma
65117	HIV disease resulting in lymphoid interstitial pneumonitis
111979	HIV disease resulting in multiple diseases CE
50076	HIV disease resulting in multiple infections
105324	HIV disease resulting in multiple malignant neoplasms
37006	HIV disease resulting in mycobacterial infection
111981	hiv disease resulting in other types of non-hodgkin lymphoma
27641	HIV disease resulting in Pneumocystis carinii pneumonia

104717	hiv disease resulting in pneumocystis jirovecii pneumonia
67575	HIV disease resulting in unspecified malignant neoplasm
8281	HIV disease resulting in wasting syndrome
71450	HIV disease resulting/unspcf infectious disease
111972	hiv infection monitoring first telephone invitation
111973	hiv infection monitoring second telephone invitation
109327	hiv infection monitoring telephone invitation
111974	hiv infection monitoring third telephone invitation
69766	HIV infection with persistent generalised lymphadenopathy
105040	hiv pos gen health check serv declind - enhanc service admin
2835	HIV positive
111971	hiv positive general health check service declined
44303	Human immunodef virus resulting in other disease
101191	human immunodeficiency virus annual review
9130	human immunodeficiency virus infection
108385	human immunodeficiency virus infection monitoring invitation
98966	human immunodeficiency virus monitoring
70869	Human immunodeficiency virus with constitutional disease
53636	Human immunodeficiency virus with neurological disease
62891	Human immunodeficiency virus with other clinical findings
101836	Human immunodeficiency virus with secondary cancers
70528	Human immunodeficiency virus with secondary infection
33943	Notification of AIDS
109513	human immunodeficiency virus drug resistance test
110374	human immunodeficiency virus type 1 subtype identification
96902	human immunodeficiency virus viral load by log rank

Smoking status

Medcode	Description	Smoking status
11788	Non-smoker	Never
33	Never smoked tobacco	Never
12957	Ex-light smoker (1-9/day)	Ex
72706	Tobacco dependence in remission	Ex
12961	Ex-trivial smoker (<1/day)	Ex
12956	Ex-heavy smoker (20-39/day)	Ex
776	Stopped smoking	Ex
97210	Ex-cigarette smoker	Ex
26470	Ex pipe smoker	Ex
90	Ex smoker	Ex
12955	Ex-moderate smoker (10-19/day)	Ex
100963	Ex-smoker annual review	Ex
12959	Ex-very heavy smoker (40+/day)	Ex
19488	Ex cigar smoker	Ex
12946	Ex-smoker - amount unknown	Ex
98447	Ex-smoker annual review - enhanced services administration	Ex
100495	Ex roll-up cigarette smoker	Ex
106359	Referral to smoking cessation service	Current
40417	Stop smoking monitor default	Current
63666	Fagerstrom test for nicotine dependence	Current
59866	Reasons for smoking scale	Current
63299	Ftnd - fagerstrom test for nicotine dependence	Current
12941	Occasional smoker	Current
10558	Current smoker	Current

47273	Motives for smoking scale	Current
12964	Keeps trying to stop smoking	Current
74907	Smoking cessation therapy	Current
104310	Current smoker annual review	Current
11527	Dna - did not attend smoking cessation clinic	Current
10211	Smoking cessation milestones	Current
62686	Minutes from waking to first tobacco consumption	Current
94958	Smoking cessation drug therapy	Current
9045	Advice on smoking	Current
49418	Rfs - reasons for smoking scale	Current
56144	[X]mental and behav dis due to use of tobacco: harmful use	Current
100099	Smoking cessation advice declined	Current
98493	Smoking cessatn monitor template complet - enhanc serv admin	Current
30762	Not interested in stopping smoking	Current
31114	Ready to stop smoking	Current
103507	Stop smoking service opportunity signposted	Current
7622	Smoking cessation advice	Current
35055	[V]tobacco abuse counselling	Current
60720	Stop smoking monitor 2nd lettr	Current
85247	Nicotine replacement therapy using nicotine inhalator	Current
90522	Smoking cessation therapy nos	Current
41042	Smoking cessation advice provided by community pharmacist	Current
1822	Very heavy smoker - 40+cigs/d	Current
12952	Smoking started	Current
98347	Current smoker annual review - enhanced services admin	Current
106391	Referral to smoking cessation service declined	Current
46321	Reason for restarting smoking	Current
104230	Smoking cessation programme declined	Current
41979	Smoking restarted	Current
12944	Light smoker - 1-9 cigs/day	Current
98154	Referral to nhs stop smoking service	Current
11356	Seen by smoking cessation advisor	Current
32572	Over the counter nicotine replacement therapy	Current
68658	Tobacco dependence nos	Current
70746	Tobacco dependence, continuous	Current
81440	Nicotine replacement therapy using nicotine patches	Current
12942	Smoker - amount smoked	Current
12947	Pipe smoker	Current
107504	Mfs - motives for smoking scale	Current
63717	Bupropion contraindicated	Current
98137	Brief intervention for smoking cessation	Current
53101	Stop smoking monitor verb.inv.	Current
89464	Nicotine replacement therapy using nicotine lozenges	Current
10742	Referral to stop-smoking clinic	Current
7130	Stop smoking monitoring admin.	Current
104185	Smoking cessation drug therapy declined	Current
12945	Rolls own cigarettes	Current
25106	Nicotine replacement therapy provided free	Current
12966	Smoking reduced	Current
108835	Tobacco dependence, episodic	Current
3568	Heavy smoker - 20-39 cigs/day	Current
61905	[X]mental and behavioural disorder due to use of tobacco	Current
42722	Stop smoking monitor 1st lettr	Current
91708	Other specified smoking cessation therapy	Current
66387	Stop smoking monitor 3rd lettr	Current
67178	Nicotine replacement therapy provided by community pharmacis	Current

24529	Nicotine replacement therapy refused	Current
32687	Tobacco dependence	Current
10184	Pregnancy smoking advice	Current
95610	Tobacco dependence, unspecified	Current
58597	Stop smoking monitor phone inv	Current
91513	Occasions for smoking scale	Current
112529	[X]mental & behav dis due to use tobacco: psychotic disorder	Current
111853	[X]mental & behav dis due to use tobacco: acute intoxication	Current
40418	Refuses stop smoking monitor	Current
18573	Referral to smoking cessation advisor	Current
102361	Referral for smoking cessation service offered	Current
12951	Smoking restarted	Current
12958	Trivial smoker - < 1 cig/day	Current
93	Cigarette smoker	Current
12240	Trying to give up smoking	Current
57639	Bupropion refused	Current
85975	Nicotine replacement therapy using nicotine gum	Current
1878	Moderate smoker - 10-19 cigs/d	Current
1823	Smoker	Current
6359	Nicotine withdrawal	Current
18926	Lifestyle advice regarding smoking	Current
32083	Stop smoking clinic admin.	Current
101338	Failed attempt to stop smoking	Current
34126	Negotiated date for cessation of smoking	Current
98245	Stop smoking face to face follow-up	Current
97643	Fagerstrom test for nicotine dependence	Current
66409	Nicotine replacement therapy contraindicated	Current
9833	Nicotine replacement therapy	Current
30423	Thinking about stopping smoking	Current
12943	Cigar smoker	Current
110692	Varenicline smoking cessation therapy offered	Current
28834	Anti-smoking monitoring admin.	Current

Alcohol status

Medcode	Readcode	Description	Alcohol status
12949	1361.00	Teetotaller	Non-drinker
12970	1361.11	Non drinker alcohol	Non-drinker
4447	1361.12	Non-drinker alcohol	Non-drinker
12979	136m.00	Current non drinker	Non-drinker
967	1367.00	Stopped drinking alcohol	Former drinker
22933	136a.00	Ex-trivial drinker (<1u/day)	Former drinker
26471	136b.00	Ex-light drinker - (1-2u/day)	Former drinker
19495	136c.00	Ex-moderate drinker - (3-6u/d)	Former drinker
19493	136d.00	Ex-heavy drinker - (7-9u/day)	Former drinker
12983	136e.00	Ex-very heavy drinker-(>9u/d)	Former drinker
385	1362.11	Drinks rarely	Occasional drinker
749	1362.12	Drinks occasionally	Occasional drinker
12971	136f.00	Spirit drinker	Moderate drinker
2689	136g.00	Beer drinker	Moderate drinker
12968	136h.00	Drinks beer and spirits	Moderate drinker
12969	136i.00	Drinks wine	Moderate drinker

956	136j.00	Social drinker	Moderate drinker
26472	136l.00	Alcohol intake within recommended sensible limits	Moderate drinker
12980	136n.00	Light drinker	Moderate drinker
12985	136o.00	Moderate drinker	Moderate drinker
44783	1d19.00	Pain in lymph nodes after alcohol consumption	Moderate drinker
24735	2577.00	O/e - breath - alcohol smell	Moderate drinker
10161	2577.11	O/e - alcoholic breath	Moderate drinker
12982	136k.00	Alcohol intake above recommended sensible limits	Heavy drinker
8999	136p.00	Heavy drinker	Heavy drinker
12984	136q.00	Very heavy drinker	Heavy drinker
19401	136r.00	Binge drinker	Heavy drinker
19494	136s.00	Hazardous alcohol use	Heavy drinker
30695	136t.00	Harmful alcohol use	Heavy drinker
94670	136w.00	Alcohol misuse	Heavy drinker
101718	136y.00	Drinks in morning to get rid of hangover	Heavy drinker
84218	13zy.00	Disqualified from driving due to excess alcohol	Heavy drinker
1399	E23..12	Alcohol problem drinking	Heavy drinker
7746	E250.00	Nondependent alcohol abuse	Heavy drinker
12271	E250.11	Drunkenness nos	Heavy drinker
27518	E250.12	Hangover (alcohol)	Heavy drinker
17777	E250.13	Inebriety nos	Heavy drinker
3782	E250.14	Intoxication - alcohol	Heavy drinker
669	E250000	Nondependent alcohol abuse, unspecified	Heavy drinker
23610	E250100	Nondependent alcohol abuse, continuous	Heavy drinker
12974	E250200	Nondependent alcohol abuse, episodic	Heavy drinker
31569	E250300	Nondependent alcohol abuse in remission	Heavy drinker
28150	E250z00	Nondependent alcohol abuse nos	Heavy drinker
9169	R103.00	[d]alcohol blood level excessive	Heavy drinker
23978	U81..00	[x]evidence of alcohol involvement determined by level of intoxication	Heavy drinker
16587	Zv11311	[v]problems related to lifestyle alcohol use	Heavy drinker

Appendix 3: PROSPERO Registration (Chapter 4)

UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

Please complete all mandatory fields below (marked with an asterisk *) and as many of the non-mandatory fields as you can then click *Submit* to submit your registration. You don't need to complete everything in one go, this record will appear in your *My PROSPERO* section of the web site and you can continue to edit it until you are ready to submit. Click *Show help* below or click on the icon
to see guidance on completing each section.
This record cannot be edited because it has been rejected

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

Cardiac Complications Following Community Acquired Pneumonia: A Systematic Review and Meta-analysis

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

English

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is

expected to commence. 24/09/2018

4. * Anticipated completion date.

Give the date by which the review is expected

to be completed. 31/07/2019

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.
Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving

only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.
This field should be updated when any amendments are made to a published record and on completion and publication of the review. If this field was pre-populated from the initial screening questions then you are not able to edit it until the record is published.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record. Vadsala Baskaran

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr Baskaran

7. * Named contact email.

Give the electronic mail address of the named contact.

vadsala.baskaran@nhs.net

8. Named contact address

Give the full postal address for the named contact.

Room B02, Clinical Sciences Building, Nottingham City Hospital, Hucknall Rd, Nottingham, NG5 1PB

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code. 07515533617

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available.

This field may be completed as 'None' if the review is not affiliated to any organisation.

University of Nottingham

Organisation web address:

https://www.nottingham.ac.uk/

11. * Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

Dr Vadsala Baskaran. University of Nottingham

Professor Tricia McKeever. University of Nottingham

Professor Wei Shen Lim. Nottingham University Hospitals NHS Trust

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members.

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

1. What is the incidence of and risk factors for cardiac complications in patients with CAP?

2. What is the mortality associated with cardiac complications in patients with CAP?

3. What are the relevant biomarkers?

16. * Searches.

Give details of the sources to be searched, search dates (from and to), and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

An initial limited search of MEDLINE has been undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe article.

The sources to be searched would include MEDLINE and Embase from inception to Dec 2018. There will be no language or publication period restrictions.The reference list of all studies selected for critical appraisal will be screened for additional studies.

17. URL to search strategy.

Give a link to a published pdf/word document detailing either the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies), or upload your search strategy.Do NOT provide links to your search results.

https://www.crd.york.ac.uk/PROSPEROFILES/123996_STRATEGY_20190131.pdf

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Cardiac complications, including acute coronary syndrome, heart failure and arrhythmia following community acquired pneumonia.

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

The current review will consider studies that enrol adult participants (18 years and above) and report cardiovascular complications associated with a clinical and radiological diagnosis of CAP. Studies which included hospital acquired pneumonia (i.e. hospital admission within the last 10 days) will be excluded.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

Exposure would be those with a clinical and radiological diagnosis of CAP (defined as symptoms and signs consistent with an acute lower respiratory tract infection associated with acute consolidation on plain radiography with no alternative diagnoses).

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

N/A

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion

and exclusion criteria.

Observational studies including prospective and retrospective cohort studies and case-control studies. Cross- sectional studies will be excluded.

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24.* Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

- What is the short-term (30-day) and long-term (1 year) effect of CAP on developing incident cardiac complications?
- What are the risk factors for developing incident cardiac complications in patients with CAP?

Timing and effect measures

The main outcomes will be measured at different time-points;30 days, 90 days and 1 year Pooled relative risks will be estimated using risk ratios and odds ratios, with 95% confidence intervals. Measures of effect adjusted for confounders will be used in preference to crude measures of effect. Rate ratios and hazard ratios will not be combined with risk ratios and odds ratios.

25.* Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate
to the review

What are the relevant biomarkers?

Timing and effect measures

N/A

26.* Data extraction (selection and coding).

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

Data will be extracted from papers included in the review using the standardized data extraction form by two independent reviewers. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer. Authors of papers will be contacted to request missing or additional data where required.

27.* Risk of bias (quality) assessment.

State whether and how risk of bias will be assessed (including the number of researchers involved and how discrepancies will be resolved), how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Selected studies will be critically appraised by two independent reviewers at the study

level for methodological quality in the review using quality assessment/ risk of bias tool created for the purpose of this study. The Newcastle-Ottawa Scale (NOS) will be used for assessing the quality of non-randomised studies in meta-analysis. Any disagreements that arise will be resolved through discussion, or with a third reviewer.

All studies, regardless of their methodological quality, will undergo data extraction and synthesis (where possible).

28.* Strategy for data synthesis.

Give the planned general approach to synthesis, e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned. It is acceptable to state that a quantitative synthesis will be used if the included studies are sufficiently homogenous.

Narrative synthesis of evidence will be conducted for all included studies. Papers will, where possible be pooled in statistical meta-analysis. A funnel plot will be generated to assess publication bias if there are 10 or more studies included in a meta-analysis. A 'summary of findings' table will be used to outline the best available evidence, highlight similarities and inconsistencies within the evidence, and subsequently formulate summary statements to describe the body of evidence.

29.* Analysis of subgroups or subsets.

Give details of any plans for the separate presentation, exploration or analysis of different types of participants (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co- morbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomised or non-randomised).

Subgroup analyses will be conducted where there are sufficient data to investigate the association of CAP and the different cardiac complications that are identified.

30.* Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review

Cost effectiveness No

Diagnostic No

Epidemiologic No

Individual patient data (IPD) meta-analysis No

Intervention No

Meta-analysis No

Methodology No

Narrative synthesis No

Network meta-analysis No

Pre-clinical No

Prevention No

Prognostic No

Prospective meta-analysis (PMA) Yes

Review of reviews No

Service delivery No

Synthesis of qualitative studies No

Systematic review Yes

Other No

Health area of the review

Alcohol/substance misuse/abuse No

Blood and immune system No

Cancer No

Cardiovascular Yes

Care of the elderly No

Child health No

Complementary therapies No

Crime and justice No

Dental No

Digestive system No

Ear, nose and throat No

Education No

Endocrine and metabolic disorders No

Eye disorders No

General interest No

Genetics No

Health inequalities/health equity No

Infections and infestations No

International development No

Mental health and behavioural conditions No

Musculoskeletal No

Neurological No

Nursing No

Obstetrics and gynaecology No

Oral health No

Palliative care No

Perioperative care No

Physiotherapy No

Pregnancy and childbirth No

Public health (including social determinants of health) No

Rehabilitation No

Respiratory disorders Yes

Service delivery No

Skin disorders No

Social care No

Surgery No

Tropical Medicine No

Urological No

Wounds, injuries and accidents No

Violence and abuse No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error. English

There is not an English language summary

32. Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

England

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

N/A

34. Reference and/or URL for published protocol.

Give the citation and link for the published

protocol, if there is one Give the link to the

published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note

that by doing so you are consenting to the file being made publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Community acquired pneumonia; cardiac complications; systematic review; meta-analysis; acute coronary syndrome; heart failure; arrhythmia

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

N/A

38. * Current review status.

Review status should be updated when the review is completed and when it is published. For newregistrations the review must be Ongoing. Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available. Give the link to the published review.

Appendix 4: SR Search terms (Chapter 4)

1. community-acquired infections/
2. Community acquired.tw.
3. 1 or 2
4. Exp pneumonia/ or pneumon*.tw.
5. 3 and 4
6. Community acquired pneumonia.mp
7. 5 or 6
8.
9. Observational study.mp. or exp observational study/ or exp epidemiologic methods/
10. Prospective study.mp. or exp prospective studies/
11. Cohort study.mp or exp cohort studies/
12. Case-control study.mp. or exp case-control studies/
13. Or/ 8-11
14. 7 and 12
15. Exp Morbidity/
16. Exp Mortality/ or "hospital mortality"/
17. Exp prognosis/
18. patient readmission/
19. survival/
20. survival analysis/
21. Exp disease-free survival/

21. (morbidity or mortality or inpatient mortality or death* or treatment outcome or prognosis or length of stay or complication* or readmission* or re-admission* or rehospitali* or re-hospitali* or survival).mp.

22. Exp cardiovascular diseases/
23. exp coronary disease/
24. exp heart failure/
25. exp arrhythmias, cardiac/
26. Exp acute coronary syndrome/
27. exp unstable angina/
28. exp myocardial infarction/
29. exp myocardial ischemia/
30. exp coronary thrombosis/
31. exp pericarditis/
32. (cardiovascular or cardiac or heart or coronary or arrhythmia* or arhythmia* or acute coronary syndrome or unstable angina or heart attack or heart failure or myocardial infarct* or myocardial isch* or pericarditis or shock*).mp.
33. or/ 14-32
34. 13 and 33

35. remove duplicates from 34
36. animals/ not humans/
37. 35 not 36

Appendix 5: Data extraction form (Chapter 4)

Reason for exclusion:

☐ Included ☐ Excluded ☐ Double-checked

Reviewer			
Lead author		**Year of publication**	
Title			
Journal			
Description / Comments			
Abstract only ☐		**Full paper** ☐	
English ☐		**Other language** ☐	

Study Details		
Type of study	**Prospective** ☐	**Retrospective** ☐
	Cohort ☐	**Other** ☐
Country		
Number of centres		
Type of centres		
Enrolment period		

Follow-up period			
Participant Details			
Inclusion criteria			
	CAP definition:		
Exclusion criteria			
Definition of cardiac complication(s)			
	With acute cardiac events	**Without acute cardiac events**	**Notes**
Average age: Mean (SD)/ median (IQR)			
Male (%)			
Number identified			
Final study number			

Results

Outcome of interest

☐ Incidence of cardiac complication(s); *new/ worsening of existing symptoms/ new and worsening symptoms*

☐ Mortality

☐ Risk factors for cardiac complication(s)

☐ Biomarkers

Time frame	Type of cardiac complication	Proportion (%)	Denominator

Time frame	Mortality rate (95% CI)	Proportion (%)	Denominator

Type of measurement	Risk factors for cardiac complications	Result (95% CI)	Confounders adjusted for

Adjusted ☐ **Unadjusted** ☐				
Risk ratio	☐			
Odds ratio	☐			
Hazard ratio	☐			

Type of biomarker	**Result (95% CI)**

Quality: Modified Newcastle Ottawa Scale (Cohort studies)

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

Selection	**Representativeness of the exposed cohort (1)** a) Truly representative of the average CAP in the community **(1)** b) Somewhat representative of the average CAP in the community **(1)** c) Selected group e.g. nurses, volunteers d) No description of the derivation of the cohort	
Selection	**Ascertainment of exposure (1)** a) Secure record (e.g. medical records, chest radiograph) **(1)** b) Structured interview **(1)** c) Written self-report d) No description e) Other	
Selection	**Demonstration that outcome of interest (i.e. cardiac complication/ worsening of existing cardiac symptom) was not present at start of study (1)** a) Yes **(1)** b) No or not explicitly stated	
***Comparability**	**Individuals in different outcome groups are comparable, based on the study design or confounders are adjusted for in the analysis (2)** a) The study controls for age **(1)** b) Study controls for other factors; sex **(1)** c) Outcome groups are not comparable on the basis of the design and analysis are not controlled for confounders Note: Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability.	
Outcome	**Assessment of outcome (i.e. cardiac complication) (1)** a) Independent or blind assessment or confirmation of the outcome by reference to secure records (medical records, ECG, chest radiograph, blood test, etc.) **(1)** b) Record linkage (e.g. ICD codes) **(1)** c) Self report (i.e. no reference to original medical records or x-rays to confirm the outcome) d) Other/ No description	
Outcome	**Adequacy of follow-up of cohorts (1)** a) Complete follow up; all subject accounted for **(1)** b) Subjects lost to follow up unlikely to introduce bias; number lost ≤ 20%, or description provided of those lost **(1)** c) Follow up rate < 80% and no description of those lost	

	d) No statement	
Total		**/ 5 or / 7**

*Used for studies which adjust for confounders

Quality: Modified Newcastle Ottawa Scale (Case-control studies)

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

Selection	**Is the case definition adequate? (1) i.e. with cardiac complication** a) yes, with independent validation (e.g. >1 person/ record/ time/ process to extract information or reference to primary record source such as chest radiograph, ECG, blood test or medical records) **(1)** b) yes, e.g., record linkage (ICD codes) or self-report with no reference to primary record c) no description	
Selection	**Representativeness of the cases (1)** a) consecutive or obviously representative series of cases **(1)** b) potential for selection biases or not stated	
Selection	**Selection of Controls (1)** a) community controls **(1)** b) hospital controls c) no description	
Selection	**Definition of Controls (1)** a) no history of disease (endpoint) **(1)** b) no description of source	
Comparability	**Comparability of cases and controls on the basis of the design or analysis (2)** a) study controls for age **(1)** b) study controls for any additional factor; sex **(1)**	
Exposure	**Ascertainment of exposure i.e. CAP (1)** a) secure record (e.g. medical records, chest radiograph) **(1)** b) structured interview where blind to case/control status **(1)** c) interview not blinded to case/control status d) written self-report or medical record only e) no description	
Exposure	**Same method of ascertainment for cases and controls (1)**	

	a) yes **(1)** b) no	
Exposure	**Non-Response rate (1)** a) same rate for both groups **(1)** b) non respondents described c) rate different and no designation	
Total		**/ 9**

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

Appendix 6: Codes for Chapter 5

Acute coronary syndrome

ICD-10	Description
I21	Acute myocardial infarction
I21.0	Acute transmural myocardial infarction of anterior wall
I21.1	Acute transmural myocardial infarction of inferior wall
I21.2	Acute transmural myocardial infarction of other sites
I21.3	Acute transmural myocardial infarction of unspecified site
I21.4	Acute subendocardial myocardial infarction
I21.9	Acute myocardial infarction; unspecified
I22	subsequent myocardial infarction
I22.0	Subsequent myocardial infarction of anterior wall
I22.1	Subsequent myocardial infarction of inferior wall
I22.8	Subsequent myocardial infarction of other sites
I22.9	Subsequent myocardial infarction of unspecified site
I23	Certain current complications following acute myocardial infarction
I23.0	haemopericardium as current complication following acute myocardial infarction
I23.1	Atrial septal defect as current complication following acute myocardial infarction
I23.2	Ventricular septal defect as current complication following acute myocardial infarction
I23.3	Rupture of cardiac wall without haemopericardium as current complication following acute myocardial
I23.4	Rupture of chordae tendineae as current complication following acute myocardial infarction
I23.5	Rupture of papillary muscle as current complication following acute myocardial infarction
I23.6	Thrombosis of atrium; auricular appendage; and ventricle as current complications following acute myocardial infarction
I23.8	Other current complications following acute myocardial infarction
I24.9	Acute ischemic heart disease, unspecified
I20.0	Unstable angina

Heart failure

ICD-10	Description
I50	Heart failure
I50.1	Left ventricular failure, unspecified
I50.2	Systolic (congestive) heart failure
I50.20	Unspecified systolic (congestive) heart failure
I50.21	Acute systolic (congestive) heart failure
I50.23	Acute on chronic systolic (congestive) heart
I50.3	Diastolic (congestive) heart failure
I50.30	Unspecified diastolic (congestive) heart failure
I50.31	Acute diastolic (congestive) heart failure
I50.33	Acute on chronic diastolic (congestive) heart failure
I50.4	Combined systolic (congestive) and diastolic (congestive) heart failure

I50.40	Unspecified combined systolic (congestive) and diastolic (congestive) heart failure
I50.41	Acute combined systolic (congestive) and diastolic (congestive) heart failure
I50.43	Acute on chronic combined systolic (congestive) and diastolic (congestive) heart failure
I50.8	Other heart failure
I50.81	Right heart failure
I50.810	…… unspecified
I50.811	Acute right heart failure
I50.813	Acute on chronic right heart failure
I50.814	…… due to left heart failure
I50.82	Biventricular heart failure
I50.83	High output heart failure
I50.84	End stage heart failure
I50.89	Other heart failure
I50.9	Heart failure, unspecified

Arrhythmia

ICD-10	Description
I47	Paroxysmal tachycardia
I47.0	Re-entry ventricular arrhythmia
I47.1	Supraventricular tachycardia
I47.2	Ventricular tachycardia
I47.9	Paroxysmal tachycardia; unspecified
I48	Atrial fibrillation and flutter
I48.0	Paroxysmal atrial fibrillation
I48.1	Persistent atrial fibrillation
I48.19	Other persistent atrial fibrillation
I48.3	Typical atrial flutter
I48.4	Atypical atrial flutter
I48.9	Unspecified atrial fibrillation and atrial flutter
I48.91	Unspecified atrial fibrillation
I48.92	Unspecified atrial flutter
I49	Other cardiac arrhythmias
I49.0	Ventricular fibrillation and flutter
I49.01	Ventricular fibrillation
I49.02	Ventricular flutter
I49.1	Atrial premature depolarization
I49.2	Junctional premature depolarization
I49.3	Ventricular premature depolarization
I49.4	Other and unspecified premature depolarization
I49.40	Unspecified premature depolarization
I49.49	Other premature depolarization
I49.5	Sick sinus syndrome
149.8	Other specific cardiac arrhythmias
149.9	Cardiac arrhythmia, unspecified

ACS

Medcode	Description
96838	[X]Acute transmural myocardial infarction of unspecif site
109035	[X]Subsequent myocardial infarction of other sites
99991	[X]Subsequent myocardial infarction of unspecified site
40429	Acute anteroapical infarction
12139	Acute anterolateral infarction
17872	Acute anteroseptal infarction
28736	Acute atrial infarction
9276	Acute coronary insufficiency
11983	Acute coronary syndrome
8935	Acute inferolateral infarction
29643	Acute inferoposterior infarction
241	Acute myocardial infarction
14658	Acute myocardial infarction NOS
9507	Acute non-Q wave infarction
10562	Acute non-ST segment elevation myocardial infarction
62626	Acute papillary muscle infarction
32854	Acute posterolateral myocardial infarction
30330	Acute Q-wave infarct
41221	Acute septal infarction
12229	Acute ST segment elevation myocardial infarction
3704	Acute subendocardial infarction
29758	Acute transmural myocardial infarction of unspecif site
19655	Angina at rest
14897	Anterior myocardial infarction NOS
23708	Atrial septal defect/curr comp folow acut myocardal infarct
13566	Attack - heart
30421	Cardiac rupture following myocardial infarction (MI)
36423	Certain current complication follow acute myocardial infarct
2491	Coronary thrombosis
26975	ECG: antero-septal infarct.
52705	ECG: lateral infarction
59032	ECG: myocardial infarct NOS
7783	ECG: myocardial infarction
8246	ECG: myocardial ischaemia
55401	ECG: subendocardial infarct
26972	ECG:posterior/inferior infarct
24126	Haemopericardium/current comp folow acut myocard infarct
16408	Healed myocardial infarction
1204	Heart attack
39655	Impending infarction
1678	Inferior myocardial infarction NOS
14898	Lateral myocardial infarction NOS
1677	MI - acute myocardial infarction
68357	Microinfarction of heart
4017	Old myocardial infarction
34803	Other acute myocardial infarction
46017	Other acute myocardial infarction NOS
5387	Other specified anterior myocardial infarction
17464	Personal history of myocardial infarction
9555	Post infarct angina
35119	Post infarction pericarditis

23892	Posterior myocardial infarction NOS
23579	Postmyocardial infarction syndrome
46112	Postoperative transmural myocardial infarction anterior wall
59189	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
59940	Ruptur chordae tendinae/curr comp fol acute myocard infarct
49735	Rupture of papillary muscle
69474	Rupture papillary muscle/curr comp fol acute myocard infarct
17689	Silent myocardial infarction
18842	Subsequent myocardial infarction
45809	Subsequent myocardial infarction of anterior wall
38609	Subsequent myocardial infarction of inferior wall
72562	Subsequent myocardial infarction of other sites
46166	Subsequent myocardial infarction of unspecified site
13571	Thrombosis - coronary
29553	Thrombosis atrium,auric append&vent/curr comp foll acute MI
63467	True posterior myocardial infarction
7347	Unstable angina
1431	Unstable angina
37657	Ventric septal defect/curr comp fol acut myocardal infarctn

Heart failure

Medcode	Description
21235	Suspected heart failure
9913	Heart failure confirmed
5155	O/E - pulmonary oedema
46672	New York Heart Assoc classification heart failure symptoms
18853	New York Heart Association classification - class I
13189	New York Heart Association classification - class II
19066	New York Heart Association classification - class III
51214	New York Heart Association classification - class IV
24503	Cardiac failure therapy
32898	Admit heart failure emergency
8464	Acute cor pulmonale
5141	Congestive cardiomyopathy
2062	Heart failure
1223	Cardiac failure
398	Congestive heart failure
2906	Congestive cardiac failure
10079	Right heart failure
10154	Right ventricular failure
9524	Biventricular failure
23707	Acute congestive heart failure
27884	Decompensated cardiac failure
11424	Compensated cardiac failure
884	Left ventricular failure
43618	Pulmonary oedema - acute
5942	Impaired left ventricular function
5255	Acute left ventricular failure
27964	Acute heart failure
4024	Heart failure NOS
17278	Cardiac failure NOS
7321	Pulmonary oedema NOS
558	Acute pulmonary oedema unspecified

48466	Acute oedema of lung, unspecified
5293	Acute pulmonary oedema NOS
66306	Heart failure as a complication of care
26242	New York Heart Assoc classification heart failure symptoms

Arrhythmia

Medcode	Description
53893	[x]other specified cardiac arrhythmias
6503	Cardiac arrhythmias
1535	Cardiac dysrhythmia nos
4044	Cardiac dysrhythmias
17597	Ecg: supraventricular arrhythmia
19707	Ecg: ventricular arrhythmia
29371	Ecg: ventricular arrhythmia nos
8651	Nodal rhythm disorder
31133	Other cardiac dysrhythmia nos
7827	Other cardiac dysrhythmias
31690	Re-entry ventricular arrhythmia
3757	Ecg: atrial fibrillation
31286	Ecg: ventricular fibrillation
9479	Implant intravenous pacemaker for atrial fibrillation
31077	Defibrillation
99338	External ventricular defibrillation
2212	Atrial fibrillation and flutter
1664	Atrial fibrillation
1268	Paroxysmal atrial fibrillation
35127	Non-rheumatic atrial fibrillation
96277	Permanent atrial fibrillation
96076	Persistent atrial fibrillation
23437	Atrial fibrillation and flutter nos
4374	Ventricular fibrillation and flutter
4827	Ventricular fibrillation
25583	Cardiac arrest-ventricular fibrillation
41916	Ventricular fibrillation and flutter nos
1757	Atrial flutter

Appendix 7: PROSPERO Registration (Chapter 6)

The effect of smoking on the risk of developing community acquired pneumonia in adults

Abby Hunter, Wei Shen Lim, Tricia McKeever, Rachael Murray, Vadsala Baskaran

1. Citation

Abby Hunter, Wei Shen Lim, Tricia McKeever, Rachael Murray, Vadsala Baskaran. The effect of smoking on the risk of developing community acquired pneumonia in adults. PROSPERO 2018 CRD42018093943 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018093943

2. Review question

The objective of this systematic review is to synthesise the best available research evidence to determine the risk of developing community acquired pneumonia in adults who currently or have ever smoked. Specifically, the review question is: what is the effect of smoking on the risk of developing community acquired pneumonia in adults? If possible we will also explore what effect stopping smoking has on risk of developing community acquired pneumonia in adults.

3. Searches

The search keywords were determined based on the Cochrane Tobacco Addiction review group terms for smoking and the BMJ Clinical Evidence study design search filters.

- Smoking, smoking cessation, tobacco, tobacco cessation, tobacco dependency, passive smoking, second hand smoke, quit smoking, cease smoking, stop smoking, give up smoking, community acquired pneumonia, CAP, cohort study, case-control study, longitudinal study, prospective study, epidemiologic methods.

The following databases will be searched:

- MEDLINE in-process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

- Embase

- PsycINFO

- Web of Science

We will hand search reference lists of included articles. Databases will be searched from inception to present, with no language restriction.

4. Types of study to be included

This review will consider observational studies including prospective and

retrospective cohort studies and case-control studies for inclusion. Cross-sectional studies will be excluded.

5. Condition or domain being studied

The condition of interest is community acquired pneumonia. Cases of pneumonia contracted outside of healthcare settings (community-acquired pneumonia) will be considered
.

6. Participants/population

The review will consider studies that include adults aged 18 years and above. Studies including participants with pre-existing medical conditions will be included.

7. Intervention(s), exposure(s)

The exposure of interest is tobacco smoking. We will exclude studies concerned with cannabis smoking.

8. Comparator(s)/control

The exposure is tobacco smoking. We will consider current smokers and ex-smokers. The control, i.e. non-exposed group will be non-smokers.

9. Main outcome(s)

Risk (reported as odds ratio, risk ratio or hazard ratio) of community acquired pneumonia in smokers and non-smokers.

10. Additional outcome(s)

None.

11. Data extraction (selection and coding)

Two reviewers will independently screen titles and abstracts as well as full text selection against the inclusion and exclusion criteria. Any disagreements will be resolved by discussion.

Covidence will be used to manage references.

A data extraction form will be developed, piloted and modified as necessary. Two reviewers will carry out the data extraction independently. Study authors will be contacted if the required information is unclear or not included in the paper where studies are published within the past 10 years.

Excel will be used for collating information on (but not limited to) the following: publication details, study characteristics (setting, study design, time frame), population characteristics (age, gender, co-morbidities), details of smoking status, estimates of effects, length of follow up, included covariates. Where multiple publications exist for the same study, the one with the most relevant outcomes will be included.

12. Risk of bias (quality) assessment

Two review authors will independently assess the risk of bias in included studies. Risk of bias for included observational studies will be assessed using the Newcastle-Ottawa scale, as recommended by the Cochrane Non-Randomized Studies Methods Working Group. Disagreements between the review authors over the risk of bias in

particular studies will be resolved by discussion.

13. Strategy for data synthesis

Narrative synthesis of evidence will be conducted for all included studies. Meta-analysis using random effects models will be conducted where possible. Pooled relative risks will be estimated using risk ratios and odds ratios, with 95% confidence intervals. Measures of effect adjusted for confounders will be used in preference to crude measures of effect. Heterogeneity between studies will be reported using visual inspection and quantified using I^2.

Subgroup analyses will be conducted where there are sufficient data to investigate different diagnostic categories of community acquired pneumonia, and also to compare ex-smokers with current and never smokers. Subgroup analysis will also be conducted to explore reasons for heterogeneity based on methodological quality (?6 vs <6), study design, and country (high versus low/middle income countries). Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

A funnel plot will be generated to assess publication bias if there are 10 or more studies included in a meta- analysis. Statistical tests for funnel plot asymmetry (Egger test, Begg test, Harbord test) will be performed where appropriate. Analyses will be conducted using Review Manager 5.

We will adhere to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) (Stroup et al, 2000) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al, 2010) throughout the review process.

14. Analysis of subgroups or subsets

Subgroup analyses will be conducted where there are sufficient data to investigate different diagnostic categories of community acquired pneumonia, and also to compare ex-smokers with current and never smokers. Subgroup analysis will also be conducted to explore reasons for heterogeneity based on methodological quality (?6 vs <6), study design, and country (high versus low/middle income countries).

15. Contact details for further information

Abby Hunter abby.hunter@nottingham.ac.uk

16. Organisational affiliation of the review

University of Nottingham

17. Review team members and their organisational affiliations

Dr Abby Hunter.
University of Nottingham
Professor Wei Shen Lim.
University of Nottingham
Professor Tricia McKeever.
University of Nottingham Dr
Rachael Murray. University
of Nottingham
Miss Vadsala Baskaran. University of Nottingham

18. Type and method of review

Meta-analysis, Systematic review

19. Anticipated or actual start date

01 November 2017

20. Anticipated completion date

01 November 2018

21. Funding sources/sponsors

This work was supported by core funding to the UK Centre for Tobacco and Alcohol Studies (www.ukctas.net) from the British Heart Foundation, Cancer Research UK, Economic and Social Research Council, Medical Research Council and the Department of Health, under the auspices of the UK Clinical Research Collaboration.

22. Conflicts of interest Language

(there is not an English language summary)

23. Country

England

24. Stage of review

Review Ongoing

25. Subject index terms status

Subject indexing assigned by CRD

26. Subject index terms

Adult; Community-Acquired Infections; Humans; Pneumonia; Risk; Smoking

27. Date of registration in PROSPERO

19 April 2018

28. Date of first submission

16 April 2018

29. Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	No
Risk of bias (quality) assessment	Yes	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

19 April 2018

30. Versions

Appendix 8: SR Search terms (Chapter 6)

MEDLINE (Ovid)

1. exp smoking/ or smok*.mp.
2. exp smoking cessation/ or smoking cessation.mp.
3. exp “tobacco use”/ or exp Tobacco/ or exp tobacco products/ or exp “tobacco use disorder”/ of tobacco.mp.
4. exp tobacco smoke pollution/ or passive smok*.mp. or second?hand smok*.mp.
5. (nicotine* or cigar*).mp.
6. cotinine*.mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Community-Acquired Infections/
9. exp pneumonia/ or pneumon.mp.
10. 8 OR 9
11. community acquired pneumonia.mp.
12. 10 OR 11
13. observational study.mp. or exp observational study/ or exp epidemiologic methods/
14. prospective study.mp. or exp prospective studies/
15. exp cohort studies/
16. case-control study.mp. or exp case-control studies/
17. 13 OR 14 OR 15 OR 16
18. 7 AND 12 AND 17
19. limit 18 to humans

Embase (Ovid)

1. exp Smoking/ or smok*.mp.
2. exp Smoking Cessation/ or smoking cessation.mp.
3. exp “Tobacco Use”/ or exp Tobacco/ or exp “Tobacco Use Disorder”/ or tobacco.mp.
4. exp Tobacco Smoke Pollution/ or passive smok*.mp. or second?hand smok*.mp.
5. (nicotine* or cigar*).mp.
6. cotinine*.mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Community-Acquired Infections/
9. exp pneumonia/ or pneumon*.mp.
10. 8 and 9
11. community acquired pneumonia.mp.
12. 10 or 11
13. observational study.mp. or exp Observational Study/ or exp Epidemiologic Methods/
14. prospective study.mp. or exp Prospective Studies/
15. exp Cohort Studies/
16. case-control study.mp. or exp Case-Control Studies
17. 13 or 14 or 15 or 16
18. 7 and 12 and 17
19. limit 18 to humans

PsycINFO (Ovid)

1. exp SMOKING CESSATION/ or smoking.mp. or exp PASSIVE SMOKING/ or exp TOBACCO SMOKING/
2. tobacco.mp.
3. second?hand smoke.mp.
4. exp NICOTINE/ or nicotine.mp.
5. cigar.mp.
6. cotinine.mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. community acquired infections.mp.
9. pneumonia.mp. or exp PNEUMONIA/
10. community acquired pneumonia.mp.
11. 8 or 9 or 10
12. exp observation methods/ or observational stud*.mp.
13. epidemiolog*.mp. or exp EPIDEMIOLOGY/
14. epidemiologic methods.mp.
15. exp Prospective Studies/ or prospective stud*.mp.
16. cohort stud*.mp.
17. case-control study.mp.
18. 12 or 13 or 14 or 15 or 16 or 17
19. 7 and 11 and 18

Web of Science

1. smoking
2. smoking cessation
3. tobacco
4. tobacco products
5. tobacco cessation
6. passive smoking
7. second hand smoke
8. nicotine
9. cigar
10. cotinine
11. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10
12. observational study
13. epidemiology
14. prospective study
15. cohort study
16. case control study
17. 12 OR 13 OR 14 OR 15 OR 16
18. community acquired infection
19. pneumonia
20. community acquired pneumonia
21. 18 AND 19
22. 20 OR 21
23. 11 AND 17 AND 22

Appendix 9: Data extraction form (Chapter 6)

☐ **Included** ☐ **Excluded** ☐ **Double checked**

Reviewer		Reason for exclusion:	
Trial ID Number		**Year of publication**	
Lead Author			
Title			
Journal			
Description / Comments (is it part of a larger study)			
Abstract Only ☐ **Full paper** ☐			

English ☐ Other language

Study Details	
Type of Study	**Prospective** ☐ **Retrospective** ☐
	RCT ☐ **Cohort** ☐ **Case -control** ☐ **Cross-sectional** ☐ **Other** ☐
Country	
Number of Centres	
Type of Centres	
Follow-up Period	

Participant Details			
	CAP	**Controls**	**Notes**
Average Age			
Male: Female Ratio			
Number Identified			
Number Enrolled			
Number lost to follow-up			
Final Study Number			

How is smoking status measured?		
Categories of smoking, e.g. ex-smoker, light smoker, heavy smoker, pack years		
How is CAP/influenza measured/defined? **List any inclusion and exclusion critieria**		

Results

Type of measurement	Comments, e.g. risk for light smokers, heavy smokers etc	Odds/Hazard/risk/rate ratio (95% CI)	Confounders adjusted for
Adjusted			
Unadjusted			

Quality: Newcastle Ottawa Scale (Cohort studies)

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

Selection	**Representativeness of the exposed cohort** a) Truly representative (1) b) Somewhat representative (1) c) Selected group d) No description of the derivation of the cohort	
Selection	**Selection of the non-exposed cohort (1)** a) Drawn from the same community as the exposed cohort (1) b) Drawn from a different source c) No description of the derivation of the non-exposed cohort	
Selection	**Ascertainment of exposure (1)** a) Secure record (e.g., surgical record) (1) b) Structured interview (1) c) Written self-report d) No description e) Other	
Selection	**Demonstration that outcome of interest was not present at start of study (1)** a) Yes (1) b) No	
Comparability	**Comparability of cohorts on the basis of the design or analysis controlled for confounders (2)** a) The study controls for age, sex and marital status (1) b) Study controls for other factors (list) _____ (1) c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders	
Outcome	**Assessment of outcome (1)** a) Independent blind assessment (1) b) Record linkage (1) c) Self report d) No description e) Other	
Outcome	**Was follow-up long enough for outcomes to occur (1)** a) Yes (1) b) No	
Outcome	**Adequacy of follow-up of cohorts (1)** a) Complete follow up- all subject accounted for (1) b) Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. (1) c) Follow up rate less than 80% and no description of those lost d) No statement	

Total		

Quality: Newcastle Ottawa Scale (Case-control studies)
Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection	**1) Is the case definition adequate?** a) yes, with independent validation * b) yes, e.g., record linkage or based on self reports c) no description	
Selection	**2) Representativeness of the cases** a) consecutive or obviously representative series of cases * b) potential for selection biases or not stated	
Selection	**3) Selection of Controls** a) community controls * b) hospital controls c) no description	
Selection	**4) Definition of Controls** a) no history of disease (endpoint) * b) no description of source	
Comparability	**1) Comparability of cases and controls on the basis of the design or analysis** a) study controls for _____ (Select the most important factor.) * b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)	
Outcome	**1) Ascertainment of exposure** a) secure record (eg surgical records) * b) structured interview where blind to case/control status * c) interview not blinded to case/control status d) written self-report or medical record only e) no description	
Outcome	**2) Same method of ascertainment for cases and controls** a) yes * b) no	
Outcome	**3) Non-Response rate** a) same rate for both groups * b) non respondents described c) rate different and no designation	
Total		

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

Appendix 10: Read codes for Chapter 7

Stop smoking interventions

Medical Readcodes

Medcode	Description
89464	Nicotine replacement therapy using nicotine lozenges
85975	Nicotine replacement therapy using nicotine gum
85247	Nicotine replacement therapy using nicotine inhalator
81440	Nicotine replacement therapy using nicotine patches
74907	Smoking cessation therapy
67178	Nicotine replacement therapy provided by community pharmacis
66387	Stop smoking monitor 3rd lettr
60720	Stop smoking monitor 2nd lettr
58597	Stop smoking monitor phone inv
53101	Stop smoking monitor verb.inv.
49418	RFS - Reasons for smoking scale
47273	Motives for smoking scale
42722	Stop smoking monitor 1st lettr
41042	Smoking cessation advice provided by community pharmacist
40418	Refuses stop smoking monitor
40417	Stop smoking monitor default
38112	Smoking cessation programme start date
34127	Smoking status at 4 weeks
34126	Negotiated date for cessation of smoking
32572	Over the counter nicotine replacement therapy
32083	Stop smoking clinic admin.
28834	Anti-smoking monitoring admin.
25106	Nicotine replacement therapy provided free
19485	Stop smoking monitor.chck done
18926	Lifestyle advice regarding smoking
18573	Referral to smoking cessation advisor
12953	Attends stop smoking monitor.
11527	DNA - Did not attend smoking cessation clinic
11356	Seen by smoking cessation advisor
10898	Smoking free weeks
10742	Referral to stop-smoking clinic
10211	Smoking cessation milestones
10184	Pregnancy smoking advice
9833	Nicotine replacement therapy
9045	Advice on smoking
7622	Smoking cessation advice
7130	Stop smoking monitoring admin.
110692	varenicline smoking cessation therapy offered
109716	issue of nicotine replacement therapy voucher
108966	smoking cessation esa monitoring template completed
106391	referral to smoking cessation service declined
106385	stop smoking invitation third sms text message
106384	stop smoking invitation second sms text message
106359	referral to smoking cessation service
105710	smoking cessation 12 week follow-up
105572	stop smoking invitation short message service text message
104310	current smoker annual review
104230	smoking cessation programme declined

104185	smoking cessation drug therapy declined
104086	stop smoking invitation first sms text message
103760	copd structured smoking assessment declined
103507	stop smoking service opportunity signposted
103400	referred for copd structured smoking assessment
103208	smoking status at 12 weeks
102951	lost to smoking cessation follow-up
102361	referral for smoking cessation service offered
101854	declined consent for smoking cessation data sharing
101851	declined consent for follow-up by smoking cessation team
101764	practice based smoking cessation programme start date
101634	consent given follow-up after smoking cessation intervention
101385	consent given for follow-up by smoking cessation team
101338	failed attempt to stop smoking
101325	declin cons follow-up evaluation after smoking cess interven
101210	consent given for smoking cessation data sharing
100099	smoking cessation advice declined
99838	recently stopped smoking
98493	smoking cessatn monitor template complet - enhanc serv admin
98347	current smoker annual review - enhanced services admin
98284	refer copd structured smoking assessment - enhanc serv admin
98283	copd structured smoking assessment declined - enh serv admin
98245	stop smoking face to face follow-up
98154	referral to nhs stop smoking service
98137	brief intervention for smoking cessation
96992	smoking cessation - enhanced services administration
94958	smoking cessation drug therapy
91708	other specified smoking cessation therapy
90522	smoking cessation therapy nos
66409	nicotine replacement therapy contraindicated
63717	bupropion contraindicated
63016	[x]bupropion causing adverse effects in therapeutic use
59866	reasons for smoking scale
57639	bupropion refused
53031	adverse reaction to nicotine
31114	ready to stop smoking
30762	not interested in stopping smoking
30423	thinking about stopping smoking
24529	nicotine replacement therapy refused
21637	stop smoking monitor admin.nos
12964	keeps trying to stop smoking
12240	trying to give up smoking
2111	health ed. - smoking

Therapy codes

Prodcode	Productname
467	Zyban 150mg modified-release tablets (glaxosmithkline uk ltd)
1248	Nicorette 10mg/ml nasal spray (pharmacia ltd)
1703	Nicorette 15mg transdermal patch (pharmacia ltd)
2876	Nicorette citrus 2mg medicated chewing gum (pfizer ltd)
3404	Niquitin 21mg transdermal patch (glaxosmithkline consumer healthcare)
3818	Nicotinell tts 30 sq cm transdermal patch (novartis consumer health uk ltd)
4166	Nicorette citrus 4mg medicated chewing gum (pfizer ltd)
4704	Niquitin 7mg transdermal patch (glaxosmithkline consumer healthcare)
4717	Niquitin 14mg transdermal patch (glaxosmithkline consumer healthcare)

5115	Bupropion 150mg modified-release tablets
5320	Nicorette 10mg inhalator (mcneil products ltd)
5440	Nicorette 10mg transdermal patch (pharmacia ltd)
5457	Nicotine 5mg/16hours transdermal patches
5479	Nicotine 10mg/16hours transdermal patches
5502	Nicotine 15mg/16hours transdermal patches
5515	Nicotine 1mg lozenge
5531	Nicotinell 1mg lozenge (novartis consumer health uk ltd)
5606	Nicotinell tts 20 sq cm transdermal patch (novartis consumer health uk ltd)
5659	Niquitin 4mg lozenges original menthol mint (omega pharma ltd)
5700	Niquitin 2mg lozenges original menthol mint (omega pharma ltd)
5758	Nicotine 4mg medicated chewing gum sugar free
5784	Nicotine 4mg lozenges sugar free
5877	Nicorette 2mg microtab (pharmacia ltd)
5944	Nicotine 10mg inhalation cartridges with device
5946	Nicotinell 2mg medicated chewing-gum (novartis consumer health uk ltd)
6018	Nicorette 5mg transdermal patch (pharmacia ltd)
6323	Nicotine 2mg medicated chewing gum sugar free
6448	Nicotine 21mg/24hours transdermal patches
6565	Niquitin fresh mint 2mg medicated chewing gum (omega pharma ltd)
6593	Niquitin mint 4mg lozenges (omega pharma ltd)
6630	Niquitin mint 2mg lozenges (omega pharma ltd)
6642	Niquitin fresh mint 4mg medicated chewing gum (omega pharma ltd)
6698	Nicotinell 2mg lozenges (glaxosmithkline consumer healthcare)
7303	Nicotinell tts 10 sq cm transdermal patch (novartis consumer health uk ltd)
7644	Nicabate 21mg transdermal patch (marion merrell dow ltd)
8571	Nicotine 500micrograms/dose nasal spray
9591	Nicotine 14mg/24hours transdermal patches
9804	Nicotine 7mg/24hours transdermal patches
9806	Nicotine 2mg lozenges sugar free
10527	Nicabate 14mg transdermal patch (marion merrell dow ltd)
10623	Nicabate 7mg transdermal patch (marion merrell dow ltd)
11718	Nicotine 2mg sublingual tablets sugar free
13048	Nicotinell 4mg medicated chewing-gum (novartis consumer health uk ltd)
25510	Nicotine 2mg mint flavour chewing-gum
25516	Nicotine 4mg mint flavour chewing-gum
25523	Nicorette 2mg mint flavour chewing-gum (pharmacia ltd)
27311	Niconil 22mg/24 hr transdermal patch (elan pharma)
27410	Champix 0.5mg/1mg 2 week treatment initiation pack (pfizer ltd)
27411	Champix 1mg tablets (pfizer ltd)
27412	Varenicline 1mg tablets and varenicline 500microgram tablets
27414	Varenicline 1mg tablets
29680	Niconil 11mg/24 hr transdermal patch (elan pharma)
31939	Nicorette 4mg mint flavour chewing-gum (pharmacia ltd)
33392	Nicotine 22mg/24 hr transdermal patch
35035	Champix 0.5mg tablets (pfizer ltd)
35089	Varenicline 500microgram tablets
36457	Nicopatch 21mg/24hours transdermal patches (pierre fabre ltd)
36618	Nicopatch 7mg/24hours transdermal patches (pierre fabre ltd)
36635	Nicopatch 14mg/24hours transdermal patches (pierre fabre ltd)
37646	Nicotine 1.5mg lozenges sugar free
37716	Nicopass 1.5mg lozenge (wockhardt uk ltd)
38958	Nicotinell 1mg lozenges (glaxosmithkline consumer healthcare)
39046	Nicorette invisi 25mg/16hours patches (mcneil products ltd)
39123	Nicotine 25mg/16hours transdermal patches
39166	Nicorette invisi 15mg/16hours patches (mcneil products ltd)

39521	Niquitin pre-quit mint 4mg lozenges (omega pharma ltd)
39572	Nicorette invisi 10mg/16hours patches (mcneil products ltd)
40617	Nicotinell tts 20 patches (glaxosmithkline consumer healthcare)
40620	Nicotinell tts 30 patches (glaxosmithkline consumer healthcare)
40683	Nicotinell tts 10 patches (glaxosmithkline consumer healthcare)
40730	Niquitin minis mint 1.5mg lozenges (omega pharma ltd)
40865	Niquitin minis mint 4mg lozenges (omega pharma ltd)
41040	Nicorette lemon 2mg microtab (mcneil products ltd)
41356	Nicorette microtab 2mg sublingual tablets (mcneil products ltd)
41368	Niquitin 21mg patches (omega pharma ltd)
41372	Niquitin clear 21mg patches (omega pharma ltd)
41376	Nicorette 15mg patches (mcneil products ltd)
41377	Nicorette original 2mg medicated chewing gum (mcneil products ltd)
41425	Nicorette freshmint 4mg medicated chewing gum (mcneil products ltd)
41426	Niquitin 7mg patches (omega pharma ltd)
41474	Nicorette 10mg patches (mcneil products ltd)
41485	Niquitin 14mg patches (omega pharma ltd)
41493	Nicorette icy white 4mg medicated chewing gum (mcneil products ltd)
41496	Nicorette 500micrograms/dose nasal spray (mcneil products ltd)
41505	Niquitin clear 14mg patches (omega pharma ltd)
41507	Niquitin clear 7mg patches (omega pharma ltd)
41753	Nicorette original 4mg medicated chewing gum (mcneil products ltd)
41765	Nicotinell mint 2mg medicated chewing gum (glaxosmithkline consumer healthcare)
41778	Nicorette fruitfusion 4mg medicated chewing gum (mcneil products ltd)
41779	Nicorette icy white 2mg medicated chewing gum (mcneil products ltd)
41801	Nicorette freshmint 2mg medicated chewing gum (mcneil products ltd)
41802	Nicorette 5mg patches (mcneil products ltd)
41808	Nicotinell fruit 4mg medicated chewing gum (glaxosmithkline consumer healthcare)
41809	Nicorette mint 4mg medicated chewing gum (mcneil products ltd)
41860	Nicotine bitartrate 2mg sublingual tablet
41864	Nicorette fruitfusion 2mg medicated chewing gum (mcneil products ltd)
41879	Nicotinell liquorice 2mg medicated chewing gum (glaxosmithkline consumer healthcare)
41881	Nicotinell classic 2mg medicated chewing gum (novartis consumer health uk ltd)
41909	Nicotinell mint 4mg medicated chewing gum (glaxosmithkline consumer healthcare)
41931	Nicotinell fruit 2mg medicated chewing gum (glaxosmithkline consumer healthcare)
42011	Nicotinell classic 4mg medicated chewing gum (novartis consumer health uk ltd)
42016	Nicorette mint 2mg medicated chewing gum (mcneil products ltd)
42047	Nicotinell liquorice 4mg medicated chewing gum (glaxosmithkline consumer healthcare)
42048	Nicotine bitartrate 1mg lozenges sugar free
42221	Nicotine 4mg lozenges sugar free (teva uk ltd)
42286	Nicotine bitartrate 2mg lozenges sugar free
44106	Niquitin minis cherry 1.5mg lozenges (omega pharma ltd)
45429	Nicorette quickmist 1mg/dose mouthspray freshmint (mcneil products ltd)
45504	Nicotine 1mg/dose oromucosal spray sugar free
45603	Nicorette freshmint 2mg lozenges (mcneil products ltd)
46588	Nicotinell icemint 2mg medicated chewing gum (novartis consumer health uk ltd)
46592	Nicorette 15mg inhalator (mcneil products ltd)
46701	Nicotinell icemint 4mg medicated chewing gum (novartis consumer health uk ltd)
46717	Nicotine 15mg inhalation cartridges with device
48620	Boots nicassist 10mg inhalator (the boots company plc)
49088	Niquitin clear 21mg patches (waymade healthcare plc)
49204	Champix 0.5mg/1mg 2 week treatment initiation pack (mawdsley-brooks & company ltd)
49305	Nicorette cools 2mg lozenges (mcneil products ltd)
49319	Nicorette cools 4mg lozenges (mcneil products ltd)
49607	Boots nicassist 15mg patches (the boots company plc)
49901	Champix 1mg tablets (waymade healthcare plc)

50487	Niquitin clear 14mg patches (waymade healthcare plc)
50541	Champix 0.5mg/1mg 2 week treatment initiation pack (sigma pharmaceuticals plc)
54102	Niquitin pre-quit clear 21mg patches (omega pharma ltd)
54574	Boots nicassist minty fresh 4mg medicated chewing gum (the boots company plc)
55417	Zyban 150mg modified-release tablets (lexon (uk) ltd)
55590	Nicotine 11mg/24 hr transdermal patch
56552	Boots nicassist minty fresh 2mg medicated chewing gum (the boots company plc)
57417	Nicorette 5mg patches (waymade healthcare plc)
57731	Nicobloc liquid (nicobloc plc)
57829	Niquitin strips mint 2.5mg oral films (omega pharma ltd)
58034	Nicotine 2.5mg orodispersible films sugar free
58410	Niquitin minis orange 1.5mg lozenges (omega pharma ltd)
58675	Boots nicassist 5mg patches (the boots company plc)
60236	Boots nicassist 10mg patches (the boots company plc)
61777	Nicotinell support icemint 4mg medicated chewing gum (glaxosmithkline consumer healthcare)
62246	Nicotinell support icemint 2mg medicated chewing gum (glaxosmithkline consumer healthcare)
65406	Nicorette fruitfusion 6mg medicated chewing gum (mcneil products ltd)
65765	Nicotine 6mg medicated chewing gum sugar free
65968	Boots nicassist 15mg inhalator (the boots company plc)
66101	Boots nicassist translucent 10mg/16hours patches (the boots company plc)
66285	Boots nicassist 21mg/24hours transdermal patches (the boots company plc)
66376	Nicotine 0.35mg lozenge
66460	Boots nicassist microtab 2mg sublingual tablets (the boots company plc)
66614	Boots nicassist 14mg/24hours transdermal patches (the boots company plc)
66778	Champix 0.5mg/1mg 4 week treatment initiation pack (pfizer ltd)
67143	Boots nicassist 2mg lozenges (the boots company plc)
67802	Nicorette 10mg patches (waymade healthcare plc)
68621	Boots nicassist 1mg lozenges (the boots company plc)
68879	Boots nicassist 10mg/ml nasal spray (the boots company plc)
71101	Nicorette 15mg patches (waymade healthcare plc)
71238	Niquitin extra fresh mint 2mg medicated chewing gum (omega pharma ltd)
71539	Niquitin extra fresh mint 4mg medicated chewing gum (omega pharma ltd)
72553	Boots nicassist translucent 25mg/16hours patches (the boots company plc)
72740	Boots nicassist fruit fresh 4mg medicated chewing gum (the boots company plc)
72950	Nicotine 7mg/24hours transdermal patches (ennogen healthcare ltd)
73322	Boots nicassist 7mg/24hours transdermal patches (the boots company plc)
73595	Nicorette quickmist 1mg/dose mouthspray cool berry (mcneil products ltd)
74163	Nicorette fruit 2mg lozenges (mcneil products ltd)

Appendix 11: Results and classification as likely pathogen or contaminant among positive cultures taken from patients (Chapter 8)

Blood culture

Likely pathogen	n	N
Coagulase negative Staphylococcus	13	6
Enterococcus spp.	8	5
Klebsiella spp.	3	2
Citrobacter koseri	3	2
Candida parapsilosis	1	1
Escherichia coli	1	1
Pseudomonas spp.	1	1
Staphylococcus aureus	1	1
Haemophilus influenzae	1	1
	32	20

Likely contaminant	n	N
Coagulase negative Staphylococcus	47	36
Propionibacterium sp.	2	2
Streptococcus oralis	1	1
Micrococcus luteus	1	1
Diphteroid bacilli	1	1
Anaerobic streptococci	1	1
Streptococcus species (Facklamia Languida)	1	1
Streptococcus parasanguinis	1	1
Granulicatella adiacens	1	1
Saccharomyces cerevisiae	1	1
Actinomyces sp.	1	1
Corynebacterium striatum	1	1
Lysinbacillus sphaericus	1	1
	60	49

Legend:

n= Number of times an organism was cultured from a test sample

N= Number of patients from who the organism was cultured in that test sample

BAL culture

Likely pathogen	n	N
Klebsiella spp.	17	14
Escherichia coli	7	5
Pseudomonas spp.	5	4
Enterobacter spp.	4	3
MRSA	4	2
Serratia marcesens	3	2
Staphylococcus aureus	3	3
Pluralibacter gergoviae	2	1
Proteus mirabilis	2	2
Citrobacter koseri	2	2
Raoultella sp.	1	1
Morganella morganii	1	1
Stenotrophomonas maltophilia	1	1
Haemophilus influenzae	1	1
	53	42

Likely contaminant	n	N
Candida spp	21	15
Enterococcus spp	2	2
Yeast	2	2
Upper respiratory tract flora	1	1
Streptococcus anginosus	1	1
	27	21

Legend:

n= Number of times an organism was cultured from a test sample

N= Number of patients from whom the organism was cultured in that test sample

Tracheal culture

Likely pathogen	n	N
Serratia marcesens	10	5
Enterobacter spp.	7	3
Escherichia coli	6	2
Klebsiella spp.	4	3
Raoultella sp.	4	1
Pseudomonas spp.	3	2
Proteus mirabilis	2	2
Staphylococcus aureus	2	2
Haemophilus influenzae	2	1
Aspergillus fumigatus	2	1
Citrobacter koseri	1	1
Acinetobacter baumanii	1	1
	44	24

Likely contaminant	n	N
Candida spp	10	6
Yeast	6	4
Mixed growth of Coliform & Candida	4	2
Respiratory commensals	2	1
Corynebacterium sp	1	1
	23	14

Legend:

n= Number of times an organism was cultured from a test sample

N= Number of patients from whom the organism was cultured in that test sample

Sputum culture

Likely pathogen	n	N
Pseudomonas spp.	19	11
Stenotrophomonas maltophilia	7	3
Escherichia coli	6	5
Klebsiella spp.	8	6
Citrobacter koseri	6	5
Enterobacter spp.	6	6
Staphylococcus aureus	7	6
Proteus mirabilis	2	2
Serratia marcesens	2	2
Burkholderia multivorans	2	1
Haemophilus influenzae	2	1
Pluralibacter gergoviae	1	1
Delftia acidovorans	1	1
Yersinia enterocolitica	1	1
Acinetobacter baumanii	1	1
	71	52

Likely contaminant	n	N
Candida spp	13	10
Enterococcus sp	2	2
Respiratory commensals	41	32
	56	44

Legend:

n= Number of times an organism was cultured from a test sample

N= Number of patients from whom the organism was cultured in that test sample