Primary and secondary care patient health record data linked to examine risk factors, mortality and antibiotic use in sepsis

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Abbreviations

APACHE-II – Acute Physiology and Chronic Health Evaluation

BMI – Body Mass Index

CCHIC – Critical Care Health Informatics Collaborative

CPRD – Clinical Practice Research Datalink

EHR – Electronic Health Record

GP – General Practice/ General Practitioner

HES – Hospital Episode Statistics

ICD – International Classification of Diseases

ICU – Intensive Care Unit

IMD – Index of Multiple Deprivation

LSOA – Lower Super Output Area

MIMIC-III – Medical Information Mart for Intensive Care

NEWS – National Early Warning Score

ONS – Office for National Statistics

qSOFA – Quick Sequential Organ Failure Assessment

SOFA – Sequential Organ Failure Assessment

SIR – Salford Integrated Record

SIRS – Systemic Inflammatory Response Syndrome

TRE – Trusted Research Environment

WHO – World Health Organisation

Abstract

Background: Sepsis is a serious and potentially life-threatening condition that occurs as a result of a dysregulated immune response to an infection. It causes significant damage to organ systems and tissues around the body and is associated with high mortality and long-term health implications. Antibiotics are vital in the management of sepsis, but in the face of increasing resistance of microorganisms there is a need to reduce and optimise consumption.
Aims: To use sources of primary and secondary care data to explore the role of antibiotics in sepsis patients. Specific aims were to (i) evaluate risk factors for developing sepsis, including demographics, comorbidities and prior antibiotic use, and to see if these risk factors differ between patients with community- and hospital-acquired sepsis. (ii) to estimate the burden of antimicrobials in sepsis patients and to relate it to short-term mortality. (iii) to evaluate the longer-term outcomes following a sepsis episode, including mortality, hospital readmission and antibiotic use, and to see if these differ between community- and hospital-acquired sepsis.

Methods: The studies used anonymised patient-level routinely collected electronic health record data from a US intensive care unit (MIMIC-III) and linked data from UK primary and secondary care (CPRD & HES). Sepsis cases were identified using either diagnostic codes or the Sepsis-3 criteria and in two of the studies were matched to population or hospital controls. Multivariable conditional logistic regression modelling was used to assess the risk factors associated with developing sepsis and time-to-event analysis including Kaplan-Meier and Cox proportional hazards regression modelling to evaluate the short-and longer-term outcomes.

Findings: The key findings of this work were that prior antibiotic use and comorbidity levels were associated with an increased risk of developing sepsis, but there were differences between patients with community- and hospital-acquired sepsis. During a sepsis ICU admission patients were exposed to an average of three different antimicrobials, with lower number of antibiotics associated with a lower risk of 30-day mortality. Patients who survived a sepsis episode experienced high rates of hospital readmission and mortality in the three years after hospital discharge, as well as increased rates of common infections and antibiotic use. There were also differences in outcomes after the sepsis episode between patients who developed sepsis in the community and hospital.

Conclusion: These studies are the first to use linked sources of primary and secondary care data and found substantive differences in risk factors and outcomes between patients with community- and hospital-acquired sepsis as well as differences by level of antibiotic use. These findings could help inform tools to help identify patients at risk of sepsis and optimise antibiotic use in these patients, which could benefit individual patients and help reduce overall consumption of antibiotics.

Declaration

I declare that no portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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Rationale for Journal Format

I have chosen to present this thesis in the Journal Format, where each of the three results chapters are written as stand-alone research papers. This was primarily to gain experience of writing for publication in peer-review journals and to speed up the process of publishing. Although I have yet to submit any of the papers for publication it is my intention to do so in the months following submission of this thesis.

Chapter 1 of this thesis gives an introduction and background around the research question, with the aims and objectives presented in chapter 2. In the third chapter I have presented the methods used in the studies, giving additional detail than is included in the following chapter. Chapters four to six are the three research papers, each with its own introduction, methods, results and discussion sections. The final chapter in this thesis is an overall discussion of the findings of the studies.

For each of the studies I have been primarily responsible for planning the studies, data cleaning and analysis, as well as writing the manuscripts. For the two studies using data from CPRD myself and my supervisor, Professor Tjeerd van Staa, developed the study and wrote the ISAC protocol for approval.

Chapter 1 – Background

1.1 Sepsis

Current international consensus defines sepsis as “life-threatening organ dysfunction caused by a dysregulated host response to infection”[1]. It is not particularly common but has a high mortality rate and can cause long-term effects in those who survive. Awareness of sepsis amongst healthcare professionals and the general public has increased in the past decade or so.

1.1.1 Mechanism

Sepsis is a complex condition and the mechanisms that cause sepsis are not yet understood fully. It occurs as a result of the body’s disrupted inflammatory and immune response to an infection with either bacteria, a virus, a parasite, or other microorganisms.

In a normal immune response, the levels of pro-inflammatory and anti-inflammatory cytokines are regulated and kept in balance, to reduce collateral damage to the body’s own tissues, but in sepsis this process becomes dysregulated and causes widespread, potentially life-threatening damage to multiple organ systems[2].

There are two immunological processes that occur during an episode of sepsis; hyper-inflammation which causes extensive damage to body tissues, and immunosuppression caused by a lower number of, and/or dysfunctional immune cells circulating[3,4]. This can make it harder to clear the initial infections and makes patients more vulnerable to secondary infections, which is thought to be a cause of increased mortality in sepsis patients in the ICU[5] and in the wider hospital[4].

There is some disagreement over the timings of these two processes, it was once thought that the hyper-inflammatory stage happened first followed by the immunosuppression, however current consensus is that the immunosuppression occurs throughout[6].

The effects of this dysregulated immune response can vary between patients and can depend on the site of the initial infection and the microorganism causing that infection[6]. The immunological and cellular pathways that occur are extremely complex and include systemic endothelial dysfunction, autophagy, vascular dysfunction and dysbiosis of the gut microbiome. Depending on whether the infecting organism is a bacteria, virus or fungus can affect the exact nature of the pathways and which components are involved[3]. The consequences of these pathways are reduced oxygen use by cells which damages organs and causes them to not function. Sepsis predominantly affects six organs or organ systems: the brain, the respiratory system, the liver, the renal system, the cardiovascular system and the haematological system[6,7]. Figure 2.1, below, summarises some of the effects of sepsis on organ systems and how these present clinically.

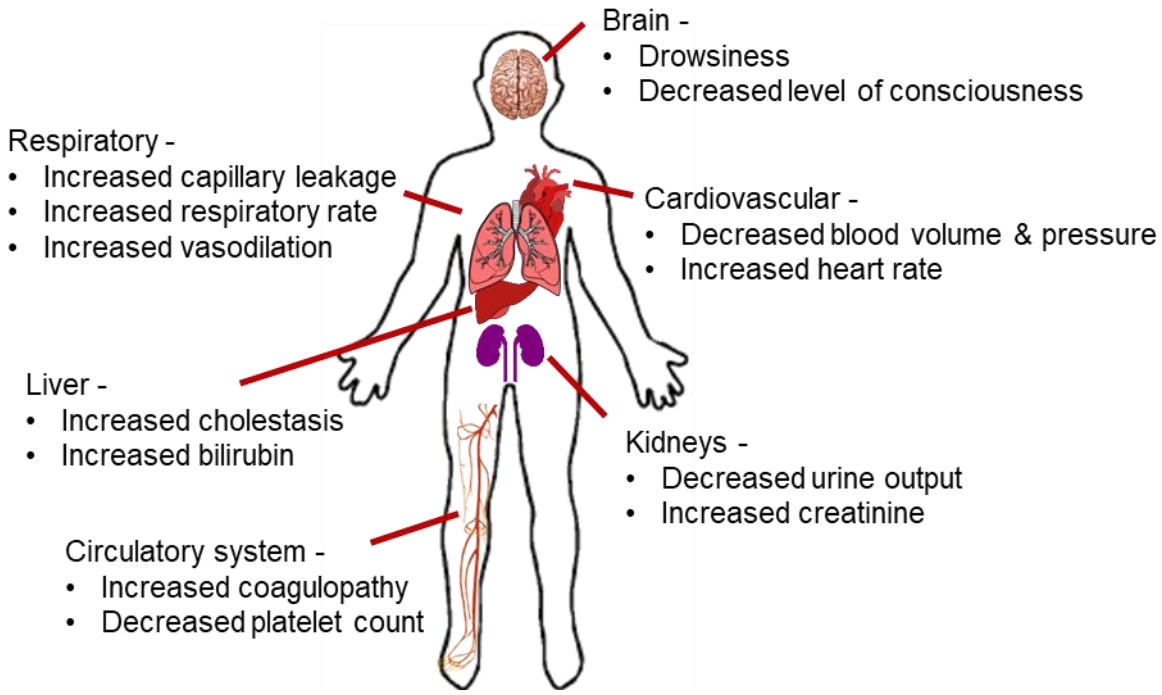


Figure 1.1 *Effects of sepsis on organ systems around the body.* Adapted from figures in Barichello et al[8] (page 27) and Sanz Codina et al[9] (page 9)

1.1.2 Guidelines

As the understanding of sepsis has developed and changed over the years so has the definition and clinical criteria. The 3rd iteration of the international consensus definitions for sepsis and septic shock, also known as Sepsis-3, was released in 2016. The consensus group was composed of 19 experts who used a comprehensive review of the existing literature and analysis of available electronic health record (EHR) data to update the definitions[10]. Previous

definitions had given a strong emphasis on inflammation and used the Systemic Inflammatory Response Syndrome (SIRS) criteria to identify sepsis, and only defined sepsis with organ dysfunction as severe sepsis. This was thought to be too broad a definition for sepsis as not all patients with high levels of inflammation are necessarily experiencing a dysregulated response. Consequently, the 2016 update got rid of severe sepsis as a term and adopted a new scoring system for quantifying organ dysfunction, the Sequential Organ Failure Assessment (SOFA) score.

The new definition for sepsis is "life-threatening organ dysfunction caused by a dysregulated host response to infection"[1]. In clinical terms this is defined as an increase in SOFA score of 2 or more alongside a suspected or confirmed infection. In the datasets used to evaluate the new criteria, which were patients with suspected infection, those with a SOFA score of >2 had an in-hospital mortality rate of 10%. Patients with septic shock are those with significant circulatory and metabolic dysfunction. The clinical criteria for identifying septic shock are the use of vasopressors to maintain a mean arterial pressure of at least 65 mmHg and a serum lactate level of more than 2 mmol/L, even with volume resuscitation. Those patients meeting the septic shock criteria had an in-hospital mortality rate of 40% in the data used in the development process[1].

The group involved with the 2016 definitions have been praised for using large datasets to validate their proposed criteria for sepsis, the first time this had been done[10,11]. However, the Sepsis-3 guidelines have faced some criticism, particularly around the use of the SOFA scoring system, as this is unlikely to be useful in areas where resources and critical care are limited[12]. The dataset used as part of the development of Sepsis-3 was from the US, so potentially not generalisable to other settings. Additionally, the measurements required for the SOFA score are invasive and whilst commonly measured within the ICU may not be routinely available elsewhere[13]. Other critiques of the guidelines focus on the lack of sensitivity, as the criteria are quite strict it is thought they may only identify more severely ill patients[14,15].

A simplified score, the qSOFA, has been developed as a screening tool which relies on three clinical measurements of respiratory rate, mental state and blood pressure, which can be used in other settings. There are a few studies looking at implementing this in lower resource settings to identify sepsis and predict mortality with varying results in terms of sensitivity and specificity, and when comparing qSOFA to using SIRS[16,17]. Other studies using modified versions of the qSOFA score or a different Early Warning Score have been shown to be effective at identifying patients at risk of sepsis or high mortality in populations in Thailand[18] and Pakistan[19]. A review by Stephen et al[13] and the paper by Rudd et al[16] highlight that there is more research that needs to be done in this area.

As well as the Sepsis-3 group there is another international consortium called the Surviving Sepsis Campaign. In 2016 they released guidelines around the management of patients with sepsis or septic shock. They undertook systematic reviews and meta-analyses on a range of aspects of sepsis care and made a number of recommendations on different treatments[20].

In the UK the National Institute for Care and Excellence (NICE) guidelines[21], last updated in 2017, do not refer to either the Sepsis-3 criteria or the use of the SOFA score. Instead, they ask clinicians to ask "could this be sepsis?" in any patient with a possible infection and provide a series of risk stratification tools for patients of different age groups. They also state that clinicians should consider the use of an early warning score, such as NEWS, which is explained further in section 1.5 of this thesis. A statement from the UK Academy of Medical Royal Colleges published in May 2022 also recommends that NEWS should be used across healthcare services in the UK to identify sepsis[22]. The comprehensive statement was put together by a working group of healthcare professionals and patient representatives, and provides recommendations to different healthcare bodies (including NICE, NHS digital and NHS trusts) on implementing their framework.

It is important for many reasons that there is a well-defined and consistently used definition of sepsis, as this underpins any research in the area. These discussions highlight the complexities of sepsis.

1.2 Prevalence and mortality

Sepsis is associated with high mortality and high costs of care, therefore representing a large burden on health care services around the world. The UK Sepsis Trust estimates that there are at least a quarter of a million patients in the UK each year suffering from sepsis, a number that has been increasing by around 10 % annually, with an estimated cost to the NHS of £1.5 - £2 billion. Estimates of mortality in the UK are between 20 – 29 %, equating to 46,000 – 67,000 deaths each year[23]. The increase in incidence of sepsis may be partly due to greater awareness of the illness amongst healthcare professionals and the public, along with the changing of definitions and the clinical diagnosis of sepsis[12].

Globally, it is difficult to get a clear picture of the full burden sepsis represents, as data from low and middle-income countries is scarce. A systematic review and meta-analysis by Fleischmann et al[12] in 2016 estimated sepsis is accountable for 5.3 million deaths each year around the world. The group updated their review in 2020 but still found a lack of data from low and middle-income countries, highlighting the need for greater surveillance[24]. A 2020 study based on the Global Burden of Disease data from 1990-2017 estimated that in 2017

there may have been 49 million cases of sepsis globally, accounting for 11 million deaths, the majority of which occurred in lower and middle -income countries[25]. Mortality from sepsis is higher in lower-income countries for a number of reasons, including lack of access to appropriate facilities and pharmaceuticals, an increased risk of nosocomial (healthcare-acquired) infection and higher levels of parasitic and viral infections within the population[26,27].

A report by WHO in 2020 called for global action on sepsis, to use consistent definitions, improve data collection and surveillance, and to develop diagnostic tools that are quick and suitable for use in low-resource settings[28].

1.3 Long term effects

Sepsis is a serious condition with a high mortality rate associated with it. Additionally, patients who survive an initial episode of sepsis are at risk of numerous longer term physical and mental health effects. This may be due to prolonged effects of the significant organ damage experienced during sepsis, or prolonged dysfunction of the patient's immune system.

Whilst there are multiple studies looking at these longer-term effects some have been critiqued for not including a control group, and not accounting for differences in health status prior to sepsis[29]. All patients who are in need of critical care are at an increased risk of mortality and prolonged health impact[30]. Without control groups and comparisons between the pre- and post-sepsis period it is difficult to attribute the outcomes specifically to sepsis[31]. A 2016 commentary piece by Cuthbertson et al[32] calls for more research using linked data sources, to look at long-term outcomes in relation to not only the period of critical illness but also pre-sepsis factors such as comorbidities.

1.3.1 Mortality

As well as a high in-hospital mortality rate, patients who survive sepsis are likely to suffer from a prolonged risk of mortality following hospital discharge. A systematic review and meta-analysis by Shankar-Hari et al[33] reported a 1-year mortality rate of 16.1% (95% CI 14.1-18.1%). They reported that age and comorbidities consistently affected mortality, however the evidence was less clear around whether there is a causal link between sepsis and late mortality.

One of few studies to use a control group was a 2016 study by Prescott et al[34] who used propensity scores to match sepsis cases over the age of 65 to three different groups of control

patients. They reported that sepsis patients had a 22% increase in late mortality compared to patients who had not been in hospital, a 10.4% increase compared to admitted patients with a non-sepsis infection and a 16.2% increase compared to patients admitted with non-infectious systemic inflammatory conditions. As they had matched patients on a number of characteristics including sex, age, race, BMI and comorbidities they concluded that the increased risk of death after sepsis could not be fully explained by their health status before sepsis.

Another study with a similar approach matched sepsis cases to groups of non-admitted people and non-sepsis admissions, also using propensity-score matching. Sepsis patients had an increased risk of mortality when compared to both groups, with a hazard ratio (HR) of 2.18 (95% CI 2.14-2.22) for the comparison between the population controls and a HR of 1.95 (95% CI 1.92-2.00) when compared to the hospital controls[35].

A third study published in 2018 by Thompson et al[36] using propensity score matching matched sepsis cases to non-sepsis patients in ICU but did not find a significant difference in 2-year survival between them (sepsis survival 60.9% vs controls survival 60.7%). This may be because even though the control patients did not have sepsis they were in ICU so potentially would have been more severely ill than the controls used in the other studies. These conflicting results again highlights the need for more research in this area[31].

1.3.2 Morbidity and quality of life

Sepsis survivors are also at risk of developing long-term physical and mental health conditions, requiring prolonged care and resulting in a shorter life expectancy[37]. Again, there are mixed results from studies looking at this. A study in the US looked at the long-term effects of severe sepsis in patients over the age of 65 and found these patients had an increased risk of experiencing a decline in both cognitive and physical ability when compared with patients who had had a non-sepsis related hospital admission[38]. Cuthbertson et al [39] followed up severe sepsis patients for 5 years after ICU discharge, looking at physical and mental quality of life measures and comparing them to population controls. They found that patients had lower physical quality of life scores but there was no significant difference in the mental quality of life scores. The study by Thompson et al [36] reported that sepsis patients had the same quality of life as non-sepsis ICU patients 6 months after discharge. Also no difference in ED visits, readmission to hospital or ICU.

Ou et al [35] reported that sepsis patients were at increased risk of major cardiovascular events, such as ischaemic stroke, myocardial infarction and ventricular arrhythmia, for up to 5 years after discharge when compared to a matched population control cohort. A 2014 study by Yende et al[40] identified a cohort of severe sepsis patients in ICU then matched them to 4 different control groups of non-sepsis ICU patients, patients hospitalised with infection, patients hospitalised without infection, and a population group. They used propensity score matching and matched patients on age, sex and health status (comorbidities and recent hospitalisations for infection) prior to hospital admission. Almost 30% of severe sepsis patients in their study experienced a cardiovascular event within 1 year, of which stroke was the most common. Compared to the control groups the ICU severe sepsis patients had a 1.9x higher risk of cardiovascular events than the population controls, a 1.1x higher risk than either of the hospital patient groups, but a similar incidence when compared to non-sepsis ICU controls. Another study looked at using troponin levels during sepsis to predict cardiovascular events in sepsis survivors who had no prior history of cardiovascular disease and found that higher levels of troponin does increase the risk[41].

A review looking at the relationship between sepsis and chronic illness concluded that people with high levels of comorbidities are at a greater risk of both developing sepsis and of worse longer-term outcomes after sepsis, but sepsis does seem to contribute to development of additional health issues[42].

1.3.3 Healthcare utilisation

There are studies assessing healthcare use after sepsis, mostly focussing on hospital readmission and use of care homes/domiciliary care etc. Shankar-Hari et al[43] conducted a systematic review and meta-analysis on rates and risk factors for readmission in patients who survive a sepsis episode. The pooled readmission rate was 21.4% at 30 days, 36.2% at 180 days and 39.0% at 1 year. The most common diagnosis for readmissions was infection-related.

Most of the studies reporting readmission rates focus on short-term periods after discharge (30 days) but there are a few looking at longer-term rates. One study reported a 1-year cumulative rate of all-cause hospital readmission of 46.9%, with a figure of 26.7% for infection-related diagnoses[44]. Prescott et al[45] reported a 42.6% readmission rate within 90 days of discharge after severe sepsis. The rate of readmissions where the primary diagnosis was infection was 11.9%, compared to 8.0% in matched acute admission control patients.

Another study by Prescott et al [46] matched severe sepsis patients with non-sepsis admissions on comorbidities, age and pre-sepsis quality of life scores. They calculated the number of days each patient spent either in their own home, in short- or long-term acute care hospitals, in a skilled nursing facility, or dead, in the year before and the year after their hospital admission. Of the sepsis patients 26.5% were readmitted within 30 days and 63% were readmitted within 1 year of discharge, and the difference in time spent in in-patient health care was 23.7 days, between the pre- and post-sepsis periods.

Liu et al in 2014[47] also compared healthcare use before and after a sepsis episode. There were 17.9% of patients readmitted to hospital within 30 days and 47.9% after 1 year. There was a significant difference in the average proportion of days patients spent in facility-based care, and this effect varied when stratifying by age group.

There are not any studies using UK data looking at healthcare use exclusively in sepsis patients. However, a 2016 study used data from Scottish ICU patients (which will include some sepsis cases along with other critical illnesses) to estimate healthcare use in the 5 years after discharge, matching ICU patients with non-ICU hospital controls on age, sex and type of admission. They defined hospital resources as elective day-cases or inpatient stays as well as emergency admissions. ICU patients had a higher amount of days in hospital than the control group, and when compared to their hospital costs for the pre-ICU period they were significantly higher after discharge[48].

All of the studies looking at healthcare use focus on hospital readmissions or time spent in care facilities. Whilst this is understandable given the high associated costs, there is a gap in the research for studies looking at the impacts on primary care services. This is important as patient contact with primary care may be the earliest opportunity to identify patients at risk of mortality or readmission.

1.3.4 Risk factors associated with long-term outcomes

A study by Shankar-Hari et al in 2020[44] using English ICU data from over 120,000 patients developed and internally validated a clinical prediction model predicting patient's risk of readmission or death, where the patient had survived a sepsis episode. The final predictors included in the model were a combination of demographic variables (age, deprivation score), pre admission variables (dependence, hospitalisation in previous year, comorbidities) and factors relating to the sepsis admission (type of admission, site of infection, blood haemoglobin level).

A previous study by the same group, using data from the same ICU audit, had looked at risk factors associated with mortality only, up to 5 years after discharge. They included a mixture of generic and sepsis-specific variables and identified that older age, high comorbidity levels, some level of dependency before admission (assistance required to perform daily activities) and longer hospital length of stay all increased risk of mortality. Additionally, the site of initial infection and the level of organ dysfunction also had an effect[49].

There are a couple of other studies, both using data from hospitals in the US, looking at factors influencing risk of readmission but only for 30-day outcomes. They both found a mixture of pre-sepsis variables and some relating to the sepsis episode as increasing the risk of readmission[50,51].

Lone et al[52] developed and validated a prediction model predicting 90-day readmission, using audit data from over 55,000 patients in Scottish ICU's, but this was in all ICU patients, not sepsis-specific. Of a combination of demographic factors, pre-illness factors and factors rating to their illness period they found that in the full cohort the pre-illness factors such as comorbidities and previous hospitalisations had higher discriminative value than the other factors. In the sub-group of patients who had no pre-existing comorbidities the factors relating to the severity of their illness were the better predictors, including the APACHE-II score, number of organs requiring support and type of admission.

1.4 Risk factors for sepsis and patient groups

1.4.1 Risk factors for developing sepsis

There are several different risk factors associated with the development of sepsis. Age is strongly associated with sepsis, with the people over the age of 85 at a significantly increased risk[53]. Patients over the age of 65 account for almost two thirds of sepsis patients in studies in both the US[54,55] and the UK[56]. New-born babies are also at a higher risk. In terms of sex, there are mixed results from studies, however, pregnant women and women who have recently given birth are known to be at an increased risk.

A number of comorbidities are associated with an increased risk of developing sepsis, as well as lifestyle factors. Commonly reported comorbidities include diabetes, stroke, lung disease, kidney disease, atrial fibrillation, deep vein thrombosis, hypertension and congestive heart failure[53,55,57–60]. High levels of alcohol use, tobacco intake and drug abuse have also been associated with increased risk of sepsis[53,55,58]. A study by Wang et al[55], which used a national

US community-based cohort, looked at the association between specific comorbidities and also at the overall number of conditions each patient had. Compared to patients with zero comorbidities patients with one comorbidity had a 1.9x higher risk of sepsis, those with five comorbidities had a 4.9x higher risk and patients with eight or more comorbidities had a 14.5x increased risk of developing sepsis.

Another study looking at multi-morbidity used latent class analysis to identify subgroups of ICU patients in a single US hospital based on demographics and comorbidities, and compare prevalence of sepsis in each group[58]. They found six different groups varying in age and comorbidity burden. The highest rates of sepsis were in the group with high levels of liver disease and alcohol abuse, followed by a group with high prevalence of complicated diabetes and renal failure. The group with the lowest prevalence of sepsis consisted of younger patients, with the lowest levels of multi-morbidity.

Frailty has also been linked to both increased risk of sepsis and worse outcomes in sepsis. A study using a national cohort of patients in the US by Mahalingham et al[61] defined frailty as the presence of at least two of the following: weakness, exhaustion or low levels of physical activity. Frailty was associated with a 1.4x higher risk of developing sepsis. Looking at the components separately, there were significant associations between weakness and low physical activity with sepsis, but not exhaustion.

People who have an impaired immune system, either due to another disease or the use of immunosuppressant drugs or chemotherapy, are at higher risk of sepsis. A 2013 study looked at the association between inflammatory biomarkers and risk of sepsis and found that levels of IL-6, E-selectin and ICAM-1 were all associated with sepsis[62].

There have been a few studies looking at the genomic aspect of sepsis, identifying distinct molecular endotypes linked to the immune response in sepsis patients[63–65]. This emerging field can be used to look at multiple aspects of the metabolic, immunological and cellular pathways that occur during sepsis, and could be used to identify patients at risk of sepsis and also predict responses to treatments[66,67].

Another emerging area is around the role of the gut microbiome in the development and outcomes of sepsis[68,69]. Disruption of the microbiome, either through previous antibiotic use[70] or infection with *Clostridium difficile*[71], has been found to be associated with an increased risk of sepsis, although neither study looked at the composition of individual's microbiomes. One study did quantify the components of microbiota of 15 patients and compared them to healthy controls, finding that the sepsis patients had a decreased overall variety and an increased quantity of a couple of rare bacterial species. It is not possible to know if this was as a result

of the sepsis and treatment or was present before they developed sepsis[72]. More research is needed in this area.

There are other factors associated with an increased risk of sepsis that relate to healthcare use. People who have a urinary catheter[73], who have had a recent hospitalisation for either a non-infection related diagnosis or an infection-related diagnosis[70], or who have had a recent hospitalisation requiring antibiotics[71] or surgical intervention[7] have all been shown to be at higher risk of sepsis. A 2019 study by Prescott et al[74] used latent class analysis to identify subgroups of sepsis patients based on their in-patient healthcare (acute care, long-term care or nursing facilities) use in the year prior to sepsis, then related this to 90-day mortality. They used three separate cohorts of patients with sepsis in hospitals across the US. The analysis identified three groups, one with "low" users, one with "rising" use, which increased in the months leading up to sepsis, and a third group of "high-use" where patients had spent a median of 118 days of the previous year at an in-patient facility. The high use group had the highest levels of comorbidity, however it was the rising use group who had increased 90-day mortality.

Another study published in 2020 by Buchman et al[75] used data from Medicare patients in all US acute care hospitals to look at the trajectories of sepsis, comparing patients with a sepsis admission to those with a non-sepsis admission. They looked at contact with healthcare in the week immediately before admission to hospital and found that over 10% of sepsis admissions had an in-patient insurance claim, compared with 8% of non-sepsis admissions.

1.4.2 Community Acquired vs Hospital Acquired

As well as differences in the definitions for patients with sepsis and sepsis shock, patients can also be grouped depending on where they developed sepsis. There is no set definition of community-acquired or hospital-acquired (or nosocomial) sepsis, so there is variation in the literature. Some studies identify patients who are admitted to hospital with sepsis as community-acquired and those who develop it at any point after as hospital-acquired. Other studies use cut-off points of either 24 or 48 hours after admission. The Centre for Disease Control in the US define a hospital-acquired infection as one that develops after 48 hours in hospital.

The majority of people who acquire sepsis do so in the community, estimates of the proportion of hospital-acquired sepsis vary between studies, from 10.1% to 53%[76–81], however the studies do vary in how they have defined it. Additionally, the studies reporting the higher percentages

were only using patients in ICU, rather than general hospital admissions[78,80]. There are many studies which either do not differentiate between the two groups, or focus on community-acquired sepsis patients only. There are differences in the two patient groups, both in terms of the types of infections they acquire and in outcomes. It is therefore important to look at them both.

Hospital-acquired sepsis is associated with higher mortality and longer hospital stays than community-acquired[77,81,82]. This may be due to patients in hospitals generally being more unwell than those in the community or that hospital patients are more likely to contract a drug-resistant infection. A 2021 study by Shah et al[80] reported in-ICU mortality rates of 18.6% and 12.9% for hospital-acquired and community-acquired sepsis patients, respectively, in over 28,000 admissions to ten UK ICU's. Another study using a large US cohort of patients in three hundred hospitals reported similar rates of 19.2% for hospital-acquired and 8.6% for community-acquired, as well as longer ICU and overall hospital lengths of stay[77]. Rothman et al used data from four different hospitals in the US and found mortality rates between 23.0% and 46.9% in the hospital-acquired sepsis group, compared to between 10.4% and 15.5% for the community-acquired sepsis group[82]. Buchman et al looked at longer term outcomes of readmission and death within 6 months of discharge from US hospitals, and reported mortality rates of 48.0% in the hospital-acquired sepsis group compared to 22.4% in the community-acquired sepsis group[75].

Within the group of patients who acquire sepsis in hospital there can also be differences in risk factors and outcomes in patients who acquire sepsis in the ICU. A study using data from the worldwide ICON audit of ICU patients found these patients are generally younger than patients who have acquired sepsis elsewhere in the hospital and are more likely to have had surgery. There was no significant difference in mortality rates however ICU-acquired patients had longer lengths of stay[83].

1.4.3 Differences in risk factors for community and hospital-acquired sepsis

In terms of risk factors for community and hospital-acquired sepsis there is not a lot of research. Most studies either do not differentiate or focus on one group or the other. There are studies that do differentiate and report the characteristics of the two groups, but do not necessarily assess whether the differences are associated with development of sepsis[84,85], focussing on their association with the outcome instead. Padro et al reported that history of stroke, myocardial infarction and liver disease was higher in hospital-acquired sepsis patients

than community-acquired sepsis patients in ICU patients from a US hospital, but levels of AIDS and dementia were higher in community sepsis patients[85].

The Rothman study mentioned above developed models in separate cohorts of community-acquired and hospital-acquired sepsis patients, to either identify sepsis on admission or predict development of sepsis whilst admitted. They included the same initial set of around 50 predictors including physiological measurements, ICD codes, laboratory test results and drug prescriptions. The final models included 6 common predictors (heart rate, diastolic blood pressure, RI score, creatinine, admitted through the emergency department and male), with the model for identifying community-acquired sepsis having an additional 5 variables (temperature, Braden score, systolic blood pressure, genitourinary assessment failure and white blood cell count) and the model for predicting hospital-acquired sepsis had an extra 3 variables (bilirubin, ICU admission and prothrombin time). They only used information recorded at the time of admission though, and only diabetes or renal disease flagged as comorbidities[82].

1.5 Recognising sepsis

Sepsis is difficult to recognise in patients, as it is a clinical syndrome with a wide range of symptoms, rather than a single disease. There are numerous clinical indicators used by clinicians, however there is no one test or biomarker that can be used to diagnose sepsis, making it difficult to distinguish between sepsis and a localised infection[86]. A qualitative study by Rhee et al [87] surveyed 94 US physicians, mostly working in critical care, providing them with case vignettes and asking them for opinions on diagnoses. They found low rates of agreement between the clinicians, highlighting how subjective sepsis recognition is.

The most common source of infection in sepsis patients is the respiratory tract, around half of all cases of sepsis initiate with pneumonia. It could also be from an infection in the urinary tract, the abdomen, a surgical site or skin and soft tissue amongst others[23,83]. Identifying the initial infection can speed up the diagnostic process and help clinicians decide on the best antimicrobial treatment to use, however it can be difficult to pinpoint the source, particularly in patients with numerous or complex health conditions[88]. A study by Abe et al[89] in patients attending emergency departments in thirty seven Japanese hospitals reported that patients who have the source of an infection misdiagnosed or unidentified have more than a 10% increase in in-hospital mortality than compared to patients whose infection is diagnosed correctly.

Identifying patients with sepsis usually involves the use of a tool such as the SOFA score or the National Early Warning Score (NEWS). Neither of these are specific to sepsis, so will be used in combination with a confirmed or suspicion of infection. NEWS is widely used across the UK, and whilst it was developed for use in secondary care it is also recommended for use in primary care and by ambulance services. NEWS uses the following clinical markers: respiration rate, oxygen saturation, blood pressure, heart rate, body temperature, consciousness and whether or not the patient is receiving oxygen or ventilation assistance. Depending on the overall score for the patient there are thresholds for increased monitoring or referral to critical care[90]. A 2019 study used a computerised NEWS model to predict the risk of sepsis, comparing the NEWS on its own with a couple of variations in data from patients in three UK hospitals. The model consisting of NEWS plus age, sex and diastolic blood pressure performed best in a cohort of emergency admissions[91]. The same group, using the same dataset, also developed and validated a slightly different model that included measurements from blood tests including creatinine, haemoglobin and urea. This model performed better than the model without blood results, however, as there can be quite a long delay in bloods being taken and receiving results the authors recommend the use of the model without these variables[92].

The SOFA score uses further tests, to assess the function of different organ systems, including arterial blood gases, bilirubin, platelet and creatinine levels. The SOFA scoring system is recommended in the international task force guidelines[1], however one study has found that the NEWS may be more effective at identifying critically ill patients[93]. As mentioned previously, the SOFA score uses measurements that are routinely collected in ICU but not in less critical areas, which may limit its use. NEWS does not require any invasive measurements so can be used more widely across healthcare.

Other physiological indicators that can be measured include serum lactate levels (sign of kidney damage), C-reactive protein levels and procalcitonin levels[86]. These biomarkers can be used as prognostic predictors, predicting sepsis patients most at risk of death. Alternatively, they can help predict a patient's response to drugs or indicate when to de-escalate antimicrobial treatment. More research is needed to fully understand the physiological pathway of sepsis and how much this can vary between patients, to make the best use of current available biomarkers and identify new ones[2,94].

Under-recognition of sepsis can have fatal consequences, with certain cases in the UK attracting national media attention. Over-diagnosis, however, also has its implications. A cohort study found that around 40 % of patients admitted to two ICU's in the Netherlands with suspected sepsis did not in fact have an infection when cases were reviewed afterward[95].

Patients treated unnecessarily with antibiotics increases the spread of antibiotic resistance as well as putting the patient at risk of not receiving effective treatment for their condition.

1.6 Non-antimicrobial treatment

Whilst antimicrobials are vital in the treatment of sepsis to combat the initial infection there are other adjuvant therapies involved to counteract the effects of organ dysfunction and support life whilst the underlying causes are being resolved. This could include vasopressors and IV fluids to increase blood volume and pressure, mechanical ventilation to counteract the reduced lung function or continuous renal replacement therapy[20]. The timing and level of all these therapeutics are thought to have a significant effect on patient outcomes and this is an area of focus for some researchers.

There are care bundles and pathways that have been developed specifically for managing patients with sepsis. As patients are at risk of deteriorating rapidly, time is of the essence and treatment should be started as soon as sepsis is suspected. The Surviving Sepsis Campaign guidelines recommend a bundle of measures and the UK Sepsis Trust have developed a pathway of 6 steps to be taken, including the administration of oxygen, IV fluids and IV antibiotics, the taking of blood cultures and the measurement of lactate levels and urine output[96,97].

There has been a lot of focus on the use of immune-modulating therapies in sepsis treatment, however, trials have been unsuccessful, an issue discussed in this review[7]. There are numerous other potential therapies currently being researched of interest in treating patients with sepsis including vitamin A[98], statins[99], drugs targeting mitochondria dysfunction[100] and monoclonal antibodies[101].

1.7 Antimicrobial treatment

The 2018 update to the Surviving Sepsis Campaign guidelines recommended that broad-spectrum antibiotics are administered within one hour of sepsis being suspected[97]. A later update, published in 2021, recommend that this occurs only in patients with septic shock or a high possibility of sepsis. For patients where sepsis is less certain, however, they advise that further investigations should be carried out then antimicrobials given within three hours if sepsis is still suspected[102]. Ideally, the infection causing pathogen would be identified, along with its susceptibility profile and a narrow-spectrum antibiotic would be prescribed to target that specific micro-organism. Waiting for microbiology test results is not always an option

though, as this would cause delays in starting antibiotics which could adversely affect the patient's outcomes. Broad-spectrum antibiotics are therefore commonly used, with treatment reviewed when microbiology results are available and switched to a narrow-spectrum antibiotic where appropriate[88]. This review should be done within 72 hours of commencing broad-spectrum antibiotic therapy[20].

Clinicians will consider several factors when prescribing empiric antimicrobial treatment, including: any comorbidities, the use of indwelling devices such as a catheter, any recent incidences of infection and whether the patient is immunosuppressed or immunocompromised[103]. They will also take into account other medications the patient is receiving, whether they have been treated with antibiotics in the past few months and whether the patient has any known drug intolerances[20]. The range of microorganisms and their laboratory-identified resistance and susceptibility patterns found in that hospital or area (so called surveillance data) will also influence the decision[104].

1.7.1 Timeliness of antimicrobials in sepsis

Timing is very important for patients with sepsis and delays in administration of antibiotics and other treatments could have a negative effect on their outcome. As mentioned above, the Surviving Sepsis Campaign guidelines recommend antimicrobials are given within one hour where patients are highly likely to have septic shock or sepsis. Whilst there are many studies showing delays in giving antimicrobials can lead to worse outcomes there is also conflicting evidence in patients with less severe sepsis.

In patients with severe sepsis or septic shock a delay in beginning antibiotic treatment has shown to be linked to higher mortality in patients with severe sepsis in the ICU[103] and emergency departments[105]. A study by Liu et al[106] found hourly delays were associated with increased odds of in-hospital mortality in over 35,000 patients admitted through emergency departments in a US state. The effects were greatest in the subgroup of patients with severe sepsis or septic shock, with a much smaller effect in patients with sepsis without shock. They had conducted a retrospective observational cohort study using EHR data and used clinical observations as well as ICD codes to identify sepsis patients. Another strength of their study included that their cohort included patients of differing sepsis severity, rather than only those requiring ICU treatment. A limitation, however, is that by conducting retrospective analyses of EHR data you have to assume that the time that the antibiotic has been recorded in the EHR is the time they were administered it. Whereas in reality there may be a delay in a decision being made and a prescription entered to the drug actually being given to the patient. Similar

results were found in a recent study using a national cohort of patients in Korean hospitals by Im et al[107] where the trend of hourly delays in treatment associated with increased mortality was seen in septic patients with shock, but not without shock. This study used the Sepsis-3 criteria to identify patients and was prospective in design, but similarly to the Liu et al study they only included patients presenting to an ED with sepsis, not those who develop it in hospital. In contrast, a study by de Groot et al[108] also looking at patients admitted through three emergency departments in the Netherlands found no association between delays in starting antibiotics and mortality, in groups of mild to severe sepsis patients. An advantage of this study was its prospective design, however, the main criteria for entry to the study was a suspicion of infection in ED then additional severity of illness criteria were applied retrospectively and did not use any of the existing sepsis criteria or guidelines. Therefore, they may have included patients with milder illness than the other studies.

There may be a number of reasons for the conflicting findings in these studies. Using retrospectively collected EHR data does usually give access to larger multi-centre cohorts, however, the criteria and diagnosis of sepsis, along with guidelines for early management of sepsis may differ significantly between centres. The different criteria for sepsis also mean that the patients included in the different studies may be quite different in terms of disease severity. Whilst RCTs tend to be more expensive to carry out the advantages of being able to control for some of these factors would perhaps be a more appropriate study to investigate early management of sepsis.

There have been a few systematic reviews and meta-analyses in this area, again with conflicting results. A systematic review and meta-analysis by Sterling et al[109] found no significant effect on mortality of quicker antimicrobial treatment in patients with severe sepsis or septic shock when pooling the results of 11 different studies. Johnston et al[110] reported a 33% reduction in mortality when antibiotics were given within 1 hour compared to when they were given after 1 hour, based on a review of 11 studies. Sherwin et al[111] reviewed studies and concluded that patients with septic shock and severe sepsis should be treated with antibiotics as soon as possible, with the greatest effect on outcomes seen in septic shock patients. Despite having similar search terms, inclusion criteria and included a mix of RCTs and observational studies the reviews did not include all the same articles.

Due to the mixed evidence in this area there are some in the field who have criticised the use of strict time periods for antibiotic administration[112–114]. There are concerns that it could lead to excess use of antibiotics, which is one of the main drivers to emerging resistance. Whilst for patients with severe sepsis or septic shock prompt treatment is necessary, it could be that for less critically ill patients, waiting for test results and identifying the infection causing

pathogen then prescribing a narrow-spectrum antibiotic may be more effective. This is reflected in the most recent update to the Surviving Sepsis Campaign guidelines where patients with the possibility of sepsis without shock are not recommended to receive antibiotics without further investigations[102]. Additionally, the recent statement from the UK Academy of Medical Royal Colleges recommends the use of NEWS to identify patients who are critically ill and use their severity score (as well as other information) to determine whether antimicrobials should be given within one, three or six hours, to allow time for further tests to confirm infection in those less severely ill patients[22].

1.7.2 De-escalation of antimicrobials

There is an ongoing debate as to how much of which type of antimicrobial drugs and how long patients should receive antibiotics for. For example, too long and it adds to the problem of antibiotic overuse, too short and it could leave the patient still vulnerable to infection. Although patients are frequently told that they must finish a course of antibiotics there is little evidence to support the fixed duration use of antibiotics, both in primary and secondary care[115].

To reduce antibiotic use in secondary care if patients are responding well to treatment then the method of administration should be reviewed, for example switching from intravenous to oral antibiotics, along with the duration and dose. Recent research has shown that certain biomarkers, such as procalcitonin, could be used to help clinicians determine whether to de-escalate treatment in patients with acute respiratory tract infections and ICU patients[116–118]. The Stop Antibiotics on guidance of Procalcitonin Study (SAPS) showed that through using procalcitonin to guide antibiotic therapy in Dutch ICU patients, duration of treatment was reduced and this was linked to a reduction in mortality[118]. A similar study by Huang et al[117] in patients in US hospitals, however, did not find any differences in antibiotic use or outcomes when using procalcitonin guided therapy in patients with lower respiratory tract infection. Both studies were prospective studies where patients were randomised to either procalcitonin-guided de-escalation or treatment as usual. The SAPS study only included ICU patients whereas the Huang study included patients admitted through the ED. The studies also differed in the levels of procalcitonin used as a threshold for de-escalation. The SAPS study used an 80% reduction from the peak procalcitonin level whereas the study by Huang et al used an absolute level of <0.25 µg per litre. These differences could explain the contrasting results. A systematic review and meta-analysis of over 6,700 patients concluded that procalcitonin-guided antibiotic therapy was associated with lower exposure and improved outcomes in

patients with acute respiratory infections, however, the authors highlight the heterogeneity of the setting and diagnoses of the included studies.

Numerous studies have shown that patients treated for shorter periods do not have worse outcomes for a range of diseases. A 2016 randomised trial for patients in Spanish hospitals with community-acquired pneumonia assigned patients to groups after 5 days of antibiotic administration, a control group continued receiving the same drug whilst patients in the intervention arm had their treatment stopped if their temperature remained below 37.8°Celsius for at least 48 hours. Treatment in the intervention group was shown to be as effective as in the control group, who received antibiotics for an average of 10 days. The experimental group had a significantly lower readmission rate[119]. Other studies have found that shorter courses of antibiotics are as effective as longer courses in patients with pyelonephritis, intra-abdominal infections and cellulitis, amongst others[120].

A task force set up by the European Society of Intensive Care Medicine conducted a review and published guidelines in 2020 on antimicrobial de-escalation in critically ill patients. They did make some recommendations however they highlighted the lack of good quality research in the area[121]. A 2020 review looked at the evidence around shorter courses and using biomarkers to optimise treatment and concluded that there is a need for more, higher-quality, research in this area[122]. The 2021 update of the Surviving Sepsis Guidelines do recommend shorter courses, daily reviews of whether to de-escalate therapy and the use of procalcitonin to guide de-escalation. All three were classed as weak recommendations, with either low or very low quality of evidence[102].

1.7.3 Appropriateness of antimicrobials

The appropriateness of antibiotic treatment in secondary care refers to whether the drug prescribed is effective at treating the disease-causing pathogen. Kumar et al[123] found around 1 in 5 patients with septic shock received inappropriate antimicrobial treatment and these patients were approximately 5 times more likely to die, in a cohort of patients from hospitals in the US, Canada and Saudi Arabia. Another study by Suberviola Cañas et al[124] looking at patients admitted to a Spanish ICU with septic shock found a significantly higher risk of mortality in patients who had received inappropriate antibiotics, but this did vary between infection types and infecting microorganism. Both studies were only assessing patients with septic shock and were retrospective in design and used a similar definition for appropriateness. Paul et al[88] conducted a systematic review and meta-analysis of 75 studies, reporting an unadjusted odds ratio of 2.11 for the effects of inappropriate empirical treatment

on mortality in sepsis patients and found similar effects when they adjusted for age and whether patients had been treated in the ICU. However, the authors do highlight the variability in results from individual studies and the need for standardised approaches to outcomes and definitions in future studies.

Micek et al[125] conducted a study in a US hospital looking at inappropriate or ineffective empiric antibiotic treatment in patients with severe sepsis and septic shock. They found that patients with community-onset sepsis who received ineffective antibiotics did not have worse mortality than those who received appropriate empiric treatment. However, for patients who acquired sepsis in the hospital there was a difference, with patients receiving ineffective antibiotics at a higher risk of death. This analysis, using Kaplan-Meier curves, did not adjust for other factors such as age, site of infection or comorbidity levels. Multivariable logistic regression identified different risk factors for ineffective treatment in the community and hospital-acquired groups. Previous IV antibiotic use is a risk factor for both groups, likely due to bacteria gaining resistance rendering empiric treatment ineffective, although a limitation of the study is that they did not have access to primary care prescriptions and were relying on patient or family recall. This study only included patients infected with Gram-negative organisms and from a single centre, so the results may not be generalizable to other patients. Other research has shown an increase in the amount of ineffective empirical antibiotic therapy and subsequent worse outcomes and associated this with an increase in multi-drug resistant microorganisms[126].

As well as choosing an appropriate type of antibiotic, clinicians also have to decide what dose to give patients. Sepsis can affect the pharmacokinetics of drugs administered through numerous mechanisms and studies have shown that usual doses may not achieve optimal concentrations once they have been absorbed into the body[127]. Sepsis biomarkers could be used to help clinicians optimise dosage. The research in this area is complex and is summarised in a recent review by Sanz Codina et al[9].

1.7.4 Antimicrobials in primary care

Whilst the majority of sepsis patients will be treated at some point in their disease process in secondary care, a high proportion of those will have developed sepsis in the community. It's therefore possible that they have had recent contact with primary care and/or received a prescription for an antibiotic. In the UK primary care is responsible for the majority of antibiotic use and is therefore the focus of some antimicrobial stewardship guidance. The focus of these is to try and reduce overall use of antibiotics without adversely affecting patients.

For patients who have recently been to their GP with a suspected infection there are a number of pathways for the subsequent development of sepsis. They may not have been prescribed an antibiotic or other antimicrobial, or they may have been prescribed an inappropriate antibiotic, either in terms of the type used or the dose. Even in patients who have been prescribed an antibiotic this may not be enough to control the initial source of infection and prevent sepsis if the initial changes to immune function have already occurred. Additionally, antibiotics are known to disrupt the gut microbiome, so this could leave patients vulnerable to a secondary infection or a resistant strain[6].

Determining whether antibiotics have been prescribed appropriately or not is complicated, and usually requires clinical expertise and prescribing guidelines[128,129]. There are some studies looking at inappropriate prescribing of antibiotics in UK primary care[130], but none linking it to sepsis. There is research, however, looking at antibiotic use in terms of overall rates and frequency and linking it to outcomes including hospitalisation for infections and sepsis.

At a GP level, van Bodegraven et al[131] found that UK practices with a higher rate of antibiotic prescribing had a lower rate of hospital admissions for infection-related complications. Another UK based study by Gulliford et al[132] however did not find any evidence that practices with lower rates of antibiotic use had higher rates of serious infection. Unlike the van Bodegraven study, this study only used GP record data to identify the outcome, so the rates may be underestimated.

On an individual patient level van Staa et al[133] used UK primary and secondary care data to look at the risk of hospital admission for an infection-related complication (including sepsis) in the 6 months after an antibiotic prescription by a GP, in relation to their antibiotic use in the 3 years prior to the prescription. For all quintiles of prior antibiotic use the risk of admission was similar in the initial 3 days following the prescription, but for the remaining time period the risk in the lower frequency groups was significantly reduced compared to patients with higher prior antibiotic use. This suggests that frequent antibiotic use could increase the risk of infection-related complications, including sepsis. Another study by Gharbi et al[134], also using UK primary care data, looked at patients diagnosed with a UTI by a GP and whether or not they were prescribed an antibiotic. Patients who did not receive a prescription or had a delayed prescription had a higher risk of a blood stream infection within 60 days. Both these studies were retrospective observational cohort studies using large national UK GP databases. Another study by Little et al[135] looked at hospital admissions and death within 30 days following a GP consultation for an uncomplicated lower respiratory tract infection. They found that there was no significant reduction in risk of adverse outcomes when antibiotics were prescribed immediately or delayed, when compared to patients who were not prescribed an antibiotic.

They did find that the rates of re-consultation were lower in the delayed antibiotic prescribing group though. This study was a prospective randomised controlled trial with a smaller cohort size than the previous studies mentioned. Additionally, they used a shorter follow-up period of 30 days, which may have underestimated the incidence of adverse outcomes.

A 2020 study by Mistry et al[136] used data from over 10 million UK GP consultations to develop a model predicting the risk of hospitalisation for an infection-related complication within 30 days of a consult for either lower or upper respiratory tract infection, or urinary tract infection. The potential predictors included age, sex, ethnicity, deprivation score and comorbidity levels. For each decile of predicted risk of admission they calculated the probability of being prescribed an antibiotic. They found that the probability of antibiotics was similar across the risk groups, so patients who were at the highest risk of admission were as likely to receive an antibiotic as patients in the lowest risk group. Validating the model in a separate dataset produced only moderate c-statistics (a measure of discrimination) and calibration.

Looking specifically at sepsis patients, a paper by Gulliford et al in 2020[137] identified patients in UK primary care data who had a consultation for a common infection and calculated the probability of sepsis within 30 days. The risk of sepsis was significantly lower in patients who were prescribed an antibiotic. They also calculated the number needed to treat (NNT) to prevent a case of sepsis, stratifying by age and frailty scores. The NNT was lower in the older age groups and the patients with a higher frailty score, as well as patients who had consulted for a urinary tract infection. A limitation of this study is that they identified episodes of sepsis in primary care records only, which could potentially underestimate the rates.

1.7.5 Antimicrobial resistance

Since the discovery of the first antibiotic, penicillin, in the 1940's by Alexander Fleming, antibiotics have become a vital tool in the fight against bacterial infections. They are used all over the world and have transformed many aspects of healthcare including surgery, cancer treatment and management of chronic conditions. In the years following the introduction of penicillin there have been numerous antibiotics of different classes brought on to the market that work via various mechanisms[138].

The problem of resistance, whereby strains of bacteria become less susceptible to antibiotics, was foreseen by Fleming and began to develop soon after their introduction, with the first cases reported in the 1950's[115]. There are different mechanisms by which bacteria can acquire and develop resistance. The spread of resistance has accelerated in the last 20 years and the

number of people with resistant infections is continuing to rise. Although there are around 20 different classes of antibiotic there have been no new classes discovered in 30 years. As some classes are becoming redundant in treating certain strains of infection there are no new ones entering the market to take their place[139].

People infected with multi-drug resistant strains of bacteria are much harder to treat and therefore have a higher mortality rate than patients with susceptible strains[140]. Using surveillance data from the EU and EEA Cassini et al[141] estimated that in Europe there are around 670,000 people treated for resistant infections each year, accounting for over 30,000 deaths each year. The incidence has been increasing since 2007 and is expected to continue to rise[141]. It is estimated that by the year 2050, AMR will claim up to 10 million lives each year around the world, more than the expected deaths from cancer, at a cost of 100 trillion US dollars to the world economy. Of these 10 million predicted deaths the majority will occur in countries in Africa and Asia, however patterns of resistance do vary within regions[139].

One of the main drivers of antibiotic resistance is overuse of antibiotics[142]. A systematic review and meta-analysis by Costelloe et al[143] concluded that use of antibiotics in primary care to treat respiratory and urinary tract infections causes resistance to the antibiotic, and that higher resistance rates were associated with longer duration of courses and repeated courses. It is therefore in the interests of both individual patients and the wider population that the spread of resistance is tackled.

There are initiatives and guidelines focussed on reducing and optimising antibiotic use across primary and secondary care in the UK, as well as educating health care professionals in infection prevention measures. The UK government released its first national action plan in 2013, which lead to a 7.3% decrease in the amount of antibiotics used. The second 5-year plan from 2019 to 2024 sets a target of reducing overall antibiotic consumption by 15% by 2024[144].

A couple of studies have looked at how prescription of antibiotics has changed over the last 10 years in the UK. Sun and Gulliford[145] used data from 102 UK GP's and found yearly decreases in overall rates and prescriptions for broad-spectrum beta-lactam antibiotics between 2014 and 2017, although this varied by indication and patient age. Balinskaite et al[146] used time series analysis to look at the impact of the quality premium initiative, whereby GPs are offered financial incentives to reduce antibiotic use, on rates of prescribing from 2013 to 2017 in English practices. They also found significant decreases in overall antibiotic use and broad-spectrum beta-lactam use after the quality premium was introduced. A strength of this study was the length of follow-up, comparing two years of prescribing data both before and after the incentive was introduced. They did not have access to data around the infection for

which the antibiotic was being prescribed though, therefore they could not examine variation by indication.

As a follow on from this study the same group also looked at whether there were any consequences in terms of patient outcomes as a result of lower antibiotic prescribing by looking at primary care consults and emergency hospital admissions for specific conditions[147]. Those conditions included complications from respiratory tract infection, urinary tract infection, intra-abdominal infection and skin infection, as well as sepsis. They found there was no reduction in GP consults or emergency admissions overall for those conditions, however there was some variation when looking at each condition individually. For sepsis, in the initial 2 years after the intervention was introduced there was no significant increase in hospital admissions, followed by a sudden large increase. The authors put this down to the introduction in 2017 of a different financial incentive initiative in UK secondary care, where screening of sepsis in emergency departments and coding of sepsis in diagnostic records was increased. A strength of this study was the linkage of primary and secondary care data to assess outcomes.

Although overall rates of prescribing have decreased there is variation amongst practices across the UK[148] and between clinicians[149]. The paper by van Staa et al compared different ways of measuring antibiotic use and found considerable variation in rates, depending on which measure is used[149]. This highlights a limitation of the studies mentioned above, as these all have used a single measure of prescribing rates.

Whilst efforts to reduce consumption of antibiotics are necessary it is important that it does not lead to adverse outcomes for patients, such as complications from an infection or an unplanned hospital admission for sepsis. When deciding whether to prescribe an antibiotic clinicians must not only weigh up the potential risks to the patient of not prescribing against the potential harm of an antibiotic, but also the targets to reduce prescribing and the patients expectations from the clinician. The attitudes of both patients and clinicians have been explored in qualitative studies by Boiko et al[150,151], with potential sepsis from not prescribing an antibiotic highlighted as a concern amongst the prescribers.

More research needs to be done into how antibiotics are prescribed, how use of antibiotics is measured and how efforts to reduce antibiotic use could impact patients. As well as targets to lower use of antibiotics there also needs to be work around reducing inappropriate prescribing and optimising antibiotic use. Identifying patients at greater risk of sepsis, particularly in relation to their antibiotic use could help clinicians decide whether or not to prescribe antibiotics.

1.8 Challenges in sepsis research

There are many challenges to overcome when carrying out research in the area of improving sepsis care. The changing definitions and different ways of identifying patients can give quite different cohorts depending on the method used. Sepsis is a very heterogeneous disease and not all patients respond to interventions in the same way.

1.8.1 Changing definitions

As discussed earlier in this review the definitions of sepsis have been discussed extensively and changed a few times over the past couple of decades. As well as implications for clinical recognition and management of sepsis this also has consequences for research. It's important for researchers to consider this when comparing results from different studies, particularly those that are not as current.

1.8.2 Identifying sepsis

Identifying sepsis retrospectively in health record data can be difficult. The most straightforward way is to use International Classification of Diseases (ICD) codes, which are diagnostic codes commonly used in secondary care. The list of ICD codes is comprehensive and granular and is updated regularly. In the UK every hospital admission will have diagnostic codes recorded as part of the discharge record, with a primary diagnosis and other contributing diagnoses. In the US ICD codes are also widely used, as part of the discharge billing process for medical insurance claims.

In the 9th version of the codes (ICD-9) there are only 2 codes, for severe sepsis and septic shock only. There are additional codes for septicaemia, which is an infection that has spread to the bloodstream. Septicaemia and sepsis have in the past been used interchangeably, but nowadays septicaemia is not commonly used. The codes in the 10th version (ICD-10) are much more comprehensive, specifying what type of underlying infection has caused the sepsis (if known) and codes for severe sepsis with and without septic shock. The 11th edition, which came into use at the beginning of 2022, reflects the updated Sepsis-3 definitions of sepsis. It no longer has a code for severe sepsis and has a more comprehensive list of codes, where there is a separate code for each type of underlying infection with and without septic shock.

As well as specific codes for sepsis, researchers have developed and validated more comprehensive lists based on ICD-9 codes. Rather than relying solely on the two explicit

codes there are two sets of criteria that identify patients with an ICD-9 code for organ dysfunction in combination with a code for an infection. Commonly referred to as the Angus[152] criteria and the Martin criteria[153], they are similar but the Angus criteria includes a higher number of codes and therefore results in a larger cohort.

A 2010 study used three different selection strategies based on ICD-9 and ICD-10 codes, including the Angus[152] and Martin[153] criteria to identify a cohort of severe sepsis patients from a hospital discharge database in Sweden. Each strategy selected a cohort of patients with differing sizes (Angus n = 12,512, Martin n = 37,990) and with different estimates of in-hospital mortality (Angus 22.1%, Martin 29.2 %)[154]. As well as selecting cohorts of differing sizes the Angus and Martin criteria selected mostly distinct sets of patients, only 16.3% of patients met both the sets of criteria. A strength of the study was the use of a nationally representative discharge database over a period of 18 years, however, there will be variation in the way sepsis was diagnosed and recorded over this time period and variation between hospitals.

An alternative method of identifying sepsis retrospectively in electronic health record data is to use clinical observations and measurements to assess whether patients meet criteria for sepsis. As the definitions and clinical criteria have changed over the years, there is a lot of variation in the exact criteria used in different studies. One of the aims of the Sepsis-3 criteria is to enable a more consistent approach in research. A 2016 review by Mariansdatter et al[155] assessed the differences in reporting of sepsis incidence, comparing studies where patients had been selected by their diagnostic code in their patient record with studies where clinical observations were used. They found that studies using clinical observations reported higher incidences of sepsis than those using ICD codes, but lower incidences of severe sepsis. The authors highlighted that there was variation in the populations, settings and time periods, which could explain some of the differences in incidence.

A more recent study by Johnson et al[156] used a US ICU dataset (MIMIC-III) to identify sepsis cohorts using different methods, including by ICD-9 codes and clinical measurements of the Sepsis-3 criteria. They identified sepsis cohorts ranging from 1,062 to 5,784 patients from the same database. Identifying patients using the Sepsis-3 criteria produced the largest cohort of patients, who had the lowest rate of in-hospital mortality, whilst the smallest, more severely ill cohort of patients had explicit ICD-9 codes for sepsis in their records. In contrast to the study using Swedish medical records mentioned above[154], this study found the Angus ICD-9 criteria identified a larger number of patients than the Martin ICD-9 criteria, however the in-hospital mortality was higher in the Martin criteria cohort which was in agreement with the other study. They also found a higher proportion of patients agreeing with both sets of criteria, at 29%. The

patients in this study were only those who had been admitted to ICU so the results may not be generalizable to other studies including patients with perhaps less severe sepsis.

Another US based study by Wang et al[157] also compared the use of hospital discharge codes vs medical record review and sepsis criteria for estimating incidence of sepsis. They reported that both the Angus and Martin criteria had low sensitivity but high specificity in identifying sepsis, and both identify patients with higher in-hospital mortality than the patients selected through chart review. The authors highlighted that no approach is better than the other, but researchers need to be aware of the limitations. This study only included patients with community-acquired sepsis though and was only in a small cohort.

There are advantages and disadvantages of both options. ICD-9 and ICD-10 codes are widely used and perhaps the most straightforward method, however, they do reflect the opinion of the treating clinicians at the time. Additionally, they are often recorded as part of the discharge process and so do not usually have date/time stamps associated with them. This can make it difficult to identify where patients have acquired sepsis.

Whilst there are advantages to using clinical criteria such as Sepsis-3, such as not being restricted to the definitions of sepsis at the time of treatment, being able to apply them retrospectively to electronic health record data does require a comprehensive and granular dataset, of which there are limited options. With increasing adoption of electronic health record systems and availability of the data collected within those, identifying sepsis using clinical criteria should become more straightforward and could be used in combination or in comparison to ICD codes.

As the majority of sepsis patients will be treated in secondary care most studies will use secondary care health records for sepsis research. There are however a couple of studies where primary care records have been used, where sepsis is an outcome being measured after either prescription for an antibiotic[137] or incidence of *Clostridium difficile* infection[158]. Rather than using ICD codes UK primary care practices use alternative code sets such as READ or SNOMED codes, depending on the type of electronic health record system being used. Patients with a record of sepsis in primary care may either have seen a GP who suspected sepsis and entered it into the record, or alternatively details of sepsis from a hospital admission can be retrospectively entered in after discharge.

A recent study by Rezel-Potts et al[56] used a combination of UK secondary and primary care records to identify sepsis patients and compare the cohorts. They identified patient cohorts of roughly the same size, however there were not many patients (20%) who had a record in both primary and secondary care within a 30-day period either side of one another. The incidence of sepsis increased in both data sources throughout the study period, 2002-2017, with the

sharpest increase between 2012 and 2017. They also used logistic regression to look at whether sex, age, deprivation or time period of diagnosis were associated with the likelihood of having concurrent diagnoses. For patients with a primary care record of sepsis, patients diagnosed more recently and not within the age range of 5-55 years were more likely to have a concurrent diagnosis in secondary care. An advantage of this study was the large cohort size and linkage of primary and secondary care datasets, however, they only looked at patient's first episode of sepsis. There are implications of this for the two studies mentioned earlier, where the outcome of sepsis is measured in primary care records only, as the incidence of sepsis may be under-estimated.

1.8.3 Heterogenous patients

One of the big challenges faced by clinicians in diagnosing and treating patients with sepsis is that it is a very heterogeneous disease. The type of pathogen and site of infection will affect the severity and pathway of the disease, as well as where the patient contracted sepsis[2]. Additionally patients differ greatly in their genetic makeup which will influence their immune response, particularly levels of inflammatory cytokines, and which organ systems are affected the most[159].

The heterogeneity of sepsis is thought to partly explain why many trials assessing treatments for sepsis have failed to show an effect[160]. There has been considerable amounts of research in to possible treatments, that target aspects of the immunological or metabolic pathways, however this still hasn't resulted in any therapies specific to sepsis. Different subgroups of patients will respond to drugs in different ways and just because a drug is not proven to work in the sepsis patient population as a whole does not mean it is not effective for certain types of patient[161]. Zhang et al[162] used latent profile analysis to identify 4 subtypes in a cohort of over 14,000 patients from the MIMIC-III database. The 4 groups of patients responded differently to administration of fluids, which was associated with differences in mortality. They included a selection of physiological variables and demographic factors, however they did not include comorbidity variables, which may potentially confound the results. Similarly, trials looking at interventions in septic patients have not had the same results as when the same treatment has been used in more critically ill patients with severe sepsis or septic shock[160].

There are multiple ways to split sepsis patients into classes, which are summarised in recent papers by DeMerle et al[66] and Prescott et al[161], and there are many things to consider depending on the research question. For example whether you are looking at differences in response to treatment or differences in outcomes. Levels of inflammatory biomarkers, clinical

observations and presence of risk factors can be used, and with recent advances in transcriptomics there are also now opportunities to include gene phenotype groupings.

Whilst efforts to look at different phenotypes of sepsis are important it is crucial that this a collaborative effort, similarly to the Sepsis-3 criteria consortium, to ensure that there is some standardisation. This, along with a more standardised approach to identifying sepsis in primary and secondary care records, would make research into sepsis more reproducible and generalizable and perhaps enable consensus to be achieved on important aspects of sepsis treatment, for example duration and de-escalation of antibiotics.

1.9 Electronic health records

1.9.1 What are they?

Electronic health record (EHR) systems are increasingly used to capture information throughout patient's interactions with health care. They are used by clinicians to keep accurate records of patient's medical history and to monitor patients, and to share information between different providers and clinicians throughout patients care pathways. It is hoped that use of EHR's will improve patient care, through enhanced sharing of information and enabling patients to easily access their own medical records.

In the UK EHR systems have been widely used in primary care since 2000 [163], but use in secondary care isn't as common. Part of the NHS long term plan, published in 2019[164], is for all NHS trusts providing secondary care to be "fully digitised" by 2024, however in 2019 it was estimated that only 10% of trusts were currently meeting this target. With adoption of electronic health record (EHR) systems increasing not only in the UK but around the world, this opens up more opportunities for research using the data collected. Exactly what data is available will depend on the type of healthcare provider (primary or secondary care) and what EHR system is being used.

Most information captured in electronic health records is coded using systems such as ICD codes for diagnostics, or the OPCS Classification of Interventions and Procedures codes. Some of these are widely used around the world, for example ICD codes, but others may be more specific to individual countries or EHR system providers. For example, in the UK most primary care practices use Read or SNOMED CT codes.

The biggest challenge with making EHR data available to researchers is protecting patient's confidentiality and privacy, meaning it is necessary to remove unique patient identifiers such

as their name, address and NHS number (or equivalent if not in UK). However, there can still be a potential risk of re-identification, particularly if a rare disease is being studied or there are a small number of patients at the extreme end of a characteristic (e.g. either very young or very elderly patients in a cohort). The data controllers have a responsibility to ensure that they minimise any potential risk, which can be done using statistical disclosure control methods.

Currently, there are a number of databases available to access for research purposes, however they can differ in the types and quality of data available, as well as how they are accessed. Some datasets can be costly and gaining approval for access can be quite lengthy. As well as accessing data through large databases it is also possible to set up data sharing agreements with individual health care providers.

1.9.2 Strengths and limitations

There are many advantages of using routinely collected health data in research for observational studies. Compared to randomised control trials (RCTs) sample sizes are generally larger as individual patient recruitment is not necessary, and it is possible to conduct research on national population-based cohorts. One of the issues with RCTs is they usually have strict inclusion and exclusion criteria, meaning results are not always generalisable to the general population of interest, with observational studies there are less strict criteria so the studies can be more representative. Studies can be done retrospectively, making them quicker and less costly than actively recruiting patients and following them up over a long period of time.

There are, however, a number of disadvantages and limitations when using EHR data for research. Unlike RCT's where specific and pre-defined data is collected, with EHR data you only have what was recorded at the time and therefore there is often a large amount of missing data. There are different types of missing data and different ways to deal with these statistically. With the strict criteria to select patients for RCTs, then randomly allocating them to an intervention or control, helps control for potential confounders. But, for observational EHR studies you are limited by what data has been collected, making adjusting for confounders and proving causality difficult. Another disadvantage is the variation in the way information is recorded either through different EHR systems or different coding systems. This can make it difficult to integrate data from different sources[165].

As the main purpose of EHR systems is not for research this means that the data extracted from them can sometimes need significant handling and cleaning before it is suitable for

analysis. A study assessed the amount of missing data and outliers in the MIMIC-III dataset for a set of vital sign measurements, and found that the amount of data deemed to be "sufficient" ranged between 60 and 90%, depending on the variable[166]. This is time consuming, however, advances in technology and development of new methodology is being used to automate and improve some processes around data extraction and integration, which should improve access to research-ready data.

1.9.3 Primary care data sources

In the UK there are a few organisations providing access to primary care records. The most commonly used is the Clinical Practice Research Datalink (CPRD). CPRD provides data from two databases from general practices across the UK using one of two EHR systems, Vision and EMIS. Advantages of CPRD are the large population coverage and representativeness, but disadvantages include variability in the way data is coded and the costs of access. As CPRD is utilised in studies in this thesis, there are more details in the Methods chapter (section 4.1.1). Similarly to CPRD the Secure Anonymised Information Linkage (SAIL) databank has GP records from practices across Wales, and contains data from over 5 million patients from 2000 onwards[167]. Users have to apply with a specific protocol to access data through a trusted research environment (TRE) and it does come at a cost, albeit a relatively low cost compared to the CPRD. The data contained within SAIL and CPRD is similar, with details of all interactions patients have with their GP, including prescriptions, referrals, diagnoses and test results. They also both offer linkage to other data sources, including secondary care, mortality statistics and disease registries data.

A new source of primary care data is now available in the UK, OpenSAFELY, which was developed in response to the COVID-19 outbreak, with the aim of enabling timely research in that area[168]. It currently provides access to data from practices using the TPP SystmOne and EMIS EHR systems. The TPP practices cover over 40% of the current UK population[169]. The team behind OpenSAFELY have taken a different approach than CPRD and SAIL in the way the data is stored and accessed. Rather than extracting data from each GP EHR system and storing it centrally then providing researchers with direct access to anonymised data sets, OpenSAFELY have developed a platform whereby the data remains with each practice. Researchers do not gain access to the real datasets, they are provided with "dummy" data with which they can develop code and algorithms, which are then submitted and run through the platform on the real data. Outputs (graphs and tables etc) are then returned to the researcher. The idea behind this approach is that it better protects patient anonymity and is

more transparent. As all the code used has been written using dummy data it can all be shared openly, so anyone can see exactly what the data is being used for. Currently OpenSAFELY is available only for research around COVID-19[170].

1.9.4 Secondary care data sources

Information around secondary care admissions in England are reported in the Hospital Episode Statistics (HES) data, which are published by NHS England. HES covers all admissions at hospitals across England since 1997/1998 and provides details of date/time of admission/discharge, diagnoses, procedures, type of admission and some details of periods of critical care[171]. This data can either be accessed separately through NHS digital or linked to primary care datasets such as CPRD. More details of HES can be found in the Methods chapter, section 4.1.1. For patients in Wales, secondary care admissions are available in the Patient Episode Database for Wales (PEDW), which also can be accessed through the SAIL databank.

A disadvantage of HES and PEDW is that they do not contain any clinical observations, test results or prescriptions so their use is limited. They do provide some critical care data, summarising levels of organ dysfunction and specific organs requiring support, but they do not contain clinical measurements. A more comprehensive source of secondary critical care data covering England, Wales and Northern Ireland is the Intensive Care National Audit and Research Centre (ICNARC) Case Mix Programme (CMP). Originally set up in 1994, the aim of the centre was to provide data on outcomes of critical care patients, to enable evaluation of care and to compare performance. ICNARC currently collect data from 4 different audits. The CMP currently receives data from 100 % of units in England, Wales and Northern Ireland, and by 2019 had over 1.8 million patients in its database. Rather than using data recorded in EHR systems participating units collect data using a form and submit it to ICNARC, who validate then analyse the data. As well as producing quarterly reports of critical care performance the data can also be accessed for research[172]. There is a separate audit covering ICUs in Scotland, published by the Scottish Intensive Care Society Audit Group, which was set up in 1995[173].

In 2007 ICNARC used the CMP dataset to develop a risk prediction model, to predict outcomes in critically ill patients[174]. This model would replace the use of the American APACHE-II scoring system, which had been shown to not be generalisable to patients in the UK[175]. In 2015 a new model was developed, using a slightly different statistical approach and

incorporating different predictors. Data from around 150,000 patients was used to develop the new model and a further 90,000 admissions were used to validate the model[176].

Whilst ICNARC does have many advantages, in its coverage and validation process, it does have its limitations. For most of the physiological parameters only one observation is recorded, either a maximum or minimum value, therefore it only gives a snapshot view of a patient's condition. Another disadvantage of ICNARC is that it only contains data from patients treated in critical care or intensive care units, meaning it is biased to a sicker population and so less generalizable to other populations. There are no data available from the rest of the patients stay in hospital and it is not currently possible to link the data to any primary care records or assess longer-term outcomes. In relation to sepsis, ICNARC does record whether patients have sepsis, using the Sepsis-3 criteria.

Patients being treated in an ICU will be being continuously monitored, with physiological measurements repeatedly being taken and any fluid or drug given to the patient recorded. An electronic healthcare system could capture much more of this data and be more useful for research. A group in the US has developed the Medical Information Mart for Intensive Care (MIMIC)-III critical data set which contains over 50,000 admissions to a critical care unit over a decade and includes a large amount of observational and laboratory data[177]. Although it represents a valuable comprehensive data source the MIMIC-III dataset mainly includes critical care data, there is limited information about the patient's stay in hospital before or after their ICU stay and there are no links to primary care data. For more details about MIMIC-III please see the Methods chapter, section 4.1.2.

In November 2019 the Society of Critical Care Medicine and the European Society of Intensive Care Medicine announced the development of a European ICU database, similar to MIMIC-III, in conjunction with Amsterdam University Medical Centers. The Amsterdam University Medical Centers database (AmsterdamUMCdb) contains data from 20,109 patients in a single ICU, from 2003-2016. As with MIMIC-III the AmsterdamUMCdb is free and relatively easy to access, however does also share the same limitations of only having data from patients in ICU and it being from a single hospital[178]. A recent systematic review by Sauer et al[179] compared the two databases and discusses in detail some of the strengths and limitations.

1.9.5 Linking data sources

As briefly mentioned above when accessing primary care data through CPRD and SAIL it is possible to link those data to secondary care and other data, such as mortality statistics,

specific disease registries, deprivation scores, mental health services and social care data. ICNARC data is now available through SAIL and CPRD too, although in CPRD it is only for patients with COVID-19. The disadvantage of using the linked data in CPRD is that it limits the sample size. CPRD contains data from practices across the UK, but HES data is only available for hospitals in England, and not all registered practices have sharing agreements to link CPRD data to HES.

There have been national attempts in England to centrally collate patient data, so clinicians can access health records from different providers in one place, however they have been unsuccessful[180]. There have been some localised projects that have achieved this aim. The Salford Integrated Record (SIR) was established in 2007 and contains data from GP practices, secondary care and mental health services from across Salford. Building on this, the Greater Manchester Care Record (GMCR) was developed and includes data from all 10 boroughs in Greater Manchester, covering around 2.8 million patients.

With regards to critical care, there have also been efforts to create an EHR system driven database, called the Critical Care Health Informatics Collaborative (CCHIC)[181]. Initially this was a joint project between 5 UK hospitals all part of the National Institute for Health Research (NIHR) Biomedical Research Centre network, with the aim of creating a database with data from multiple ICU's that could be linked together. Collection of data began in 2014 and contains granular data from the EHR system, including physiological measurements and treatments administered, as well as summary data from ICNARC. Between 2014 and 2017 data from just over 18,000 patients was collected, amounting to more than 60 million data points.

Currently, the critical care data can be linked to other hospital admission data, including ICNARC. The intention is to further develop CCHIC and enable linkage to other data sources, such as mortality data (ONS) and primary care data, to create a "cradle to grave perspective of health for patients who experience critical illness"[181]. An advantage of the way in which CCHIC collects the data from the EHR systems means it is not specific to one system, the initial ICU's taking part used two different ones. This could also be further expanded in the future so other EHR systems can contribute. The CCHIC team also place an emphasis on an open source approach to using their data including creating a package to be used when handling the data in R (*cleanEHR*[182]), that they hope will enable researchers without a programming background to be able to use the data.

The group behind the SAIL databank has also recently published a new methodology for linking data sources from across primary care and secondary care, called INTEGRATE[183], with the aim of enabling more research in critical care areas. There are two stages to the

process, which can be used within a TRE. The first step identifies patients in the PEDW critical care and ICNARC datasets and integrates those using a unique pseudo-anonymised patient ID and the date of admission to critical care, along with demographic and death (if applicable) details. Following this, dates of other hospital admissions and primary care consultations within a certain time frame of the critical care period are extracted and added to the dataset, giving a complete timeline of patient's care pathways. Additional data around the admissions and primary care can then be accessed. Whilst this is an improvement in access to linked primary, secondary and critical care data, there is still a gap for complete clinical observations from an EHR system, like in CCHIC.

Another example of how advances in methodology and technology are being used to improve EHR access is the Critical carE Database for Advanced Research (CEDAR), developed in the US. They have developed an automatic method to extract ICU data from an EHR system, link to non-ICU data for the same admission and transform the data so it is "cleaner" and ready for research[184].

These advancements in methodology and automation, and the development of platforms such as OpenSAFELY present many more opportunities for research, not only in relation to sepsis but many complex conditions and diseases that require care from multiple providers. As well as access to more data sources there is also emphasis on open source and resource sharing (particularly for MIMIC-III, OpenSAFELY and CCHIC), which will help make research more reproducible.

1.10 Electronic health record data in sepsis research

There are already a number of studies using EHR data in the sepsis and critical care literature, and this will only increase as more datasets are made available to researchers. There are a number of reviews discussing the potential for "big data" to improve different aspects of critical care and its role in precision medicine[185–188].

EHR data can be used to address a wide range of research questions, from descriptive epidemiological studies, assessing impact of an intervention or looking at outcomes following a procedure. They use a variety of methods including traditional statistical/epidemiological techniques and machine learning/artificial intelligence. These data sources can also be used to develop and validate algorithms designed to be used in clinical practice, for example using the NEWS score to predict patient's risk of sepsis[91] and the ICNARC model predicting risk of poor outcomes in ICU patients[176].

When the international task force was defining the new Sepsis-3 guidelines in 2016 they used EHR data for over 4 million hospital admissions at hospitals in the US to validate the proposed criteria and definitions[10,189]. Previous iterations of the guidelines had not taken this approach. There have been a few studies where the Sepsis-3 criteria have been applied to other EHR sources, including MIMIC-III[156] and a recent study by Shah et al looking at the feasibility of applying the Sepsis-3 criteria to the CCHIC data[80].

There are many examples of where EHR data research has been applied in the sepsis/critical care area. A few examples are noted here, demonstrating the range of research questions to be addressed and analytical techniques that can be used.

A couple of studies have used clustering techniques such as latent class analysis to identify subgroups within cohorts of sepsis patients, based on demographic, comorbidity and acute illness measures. Zador et al[58] applied latent class analysis to sepsis patients in MIMIC-III and identified six subgroups of varying disease severity. Knox et al[190] used a self-organising maps method to identify clusters of sepsis patients in ICU records from three hospitals in the US.

Faisal et al[91] used EHR data to validate an automated computerised NEWS to identify sepsis patients after an emergency admission to hospital. They had data from two separate hospitals, using one dataset to develop the model and the other to validate it. A 2021 study by Tarabichi et al[191] assessed whether the introduction of a sepsis early warning model integrated into the hospital EHR system had an impact on how quickly patients were prescribed an antibiotic. They randomised patients to either standard care or use of the early warning score flag, which was displayed on the system and triggered an alert sent to the pharmacist. Patients in the intervention group received antibiotics quicker than those in the standard care group, and experienced a higher number of days alive and out of hospital in the 28 days following admission.

A study by Tartof et al[192] used data from a healthcare group covering 14 hospitals in the USA to develop risk scores predicting patient's resistance to carbapenem and extended spectrum beta-lactamase antibiotics in patients with *Pseudomonas aeruginosa* infection[192]. Another study using MIMIC-III data used reinforcement learning techniques to develop a tool the authors have termed the "AI Clinician", which recommends doses of fluids and vasopressors to be given to sepsis patients[193].

Shankar-Hari et al[44] used ICNARC data to develop and validate a clinical risk score to predict 1-year hospital readmission in patients who survive an initial sepsis episode to hospital discharge. They used multivariable logistic regression and included predictors of age, comorbidity score, type of infection and admission, as well as blood haemoglobin levels. A

risk score assigning points to the different predictors was developed using the odds ratios from the model, then decision curve analysis used to determine the thresholds for the score.

A proof-of-concept study published in 2020 by De Oliveira et al[194] used a technique called "bow-tie" pathway discovery analysis to look at the clinical pathways surrounding a sepsis event. They identified patients with incident sepsis in HES data then used process mining to identify admissions and most frequent diagnoses in the 2 year period and 1 year period after sepsis. The authors discuss the potential to apply the methodology to linked primary and secondary care datasets such as SAIL.

1.11 Conclusion

Sepsis is a serious condition with high mortality rates and long term health impacts. Antibiotics are crucial in the management of sepsis, however, in the face of growing resistance to these drugs there are efforts to reduce and optimise their use.

Whilst there is a large amount of research looking at sepsis there are some gaps. There are few studies comparing patients with community-acquired and hospital-acquired sepsis and few using large population-based datasets. As sepsis is largely recognised and managed in hospitals it is understandable that most research focuses on sepsis in the acute setting, however, the majority of patients are admitted with sepsis have contracted it in the community. The role of primary care is therefore important in the pathway of sepsis patients but there is little research looking at this. This means there may be potential missed opportunities to identify patients at risk of sepsis and treat infections with antibiotics more effectively, to prevent sepsis from occurring.

Additionally, the role of primary care in sepsis survivors is under researched. Most of the research on long term consequences focuses on readmission to hospital or use of long-term care facilities. There are no studies using UK primary care data to see what the burden of sepsis patients is in terms of their antibiotic consumption following a sepsis admissions.

With use of EHR systems increasing there is a growing amount of data available for research and possibilities to link data from different providers. The aims of this thesis, therefore, were to explore the feasibility of using some of these EHR data sources to focus on the use of antibiotics throughout three stages of the sepsis pathway, in the periods before, during, and after a hospital admission for sepsis.

1.12 References

1. Singer, M. *et al.* The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* **315**, 801 (2016).
2. Talisa, V. B., Yende, S., Seymour, C. W. & Angus, D. C. Arguing for Adaptive Clinical Trials in Sepsis. *Front Immunol* **9**, 1502 (2018).
3. Dolin, H. H., Papadimos, T. J., Chen, X. & Pan, Z. K. Characterization of Pathogenic Sepsis Etiologies and Patient Profiles: A Novel Approach to Triage and Treatment. *Microbiol Insights* **12**, 117863611882508 (2019).
4. Hotchkiss, R. S., Monneret, G. & Payen, D. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. *Nat Rev Immunol* **13**, 862–874 (2013).
5. van Vught, L. A. *et al.* Incidence, Risk Factors, and Attributable Mortality of Secondary Infections in the Intensive Care Unit After Admission for Sepsis. *JAMA* **315**, 1469 (2016).
6. Lazzaro, A. *et al.* The Interplay between Host Defense, Infection, and Clinical Status in Septic Patients: A Narrative Review. *International Journal of Molecular Sciences 2022, Vol. 23, Page 803* **23**, 803 (2022).
7. Hotchkiss, R. S. *et al.* Sepsis and septic shock. *Nat Rev Dis Primers* **2**, 16045 (2016).
8. Barichello, T., Generoso, J. S., Singer, M. & Dal-Pizzol, F. Biomarkers for sepsis: more than just fever and leukocytosis—a narrative review. *Critical Care 2022 26:1* **26**, 1–31 (2022).
9. Sanz Codina, M., Zeitlinger, M., Codina, M. S., Sanz Codina, M. & Zeitlinger, M. Biomarkers Predicting Tissue Pharmacokinetics of Antimicrobials in Sepsis: A Review. *Clinical Pharmacokinetics 2022 61:5* **61**, 593–617 (2022).
10. Shankar-Hari, M. *et al.* Developing a new definition and assessing new clinical criteria for Septic shock: For the third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA - Journal of the American Medical Association* **315**, 775–787 (2016).
11. Seymour, C. W. *et al.* Assessment of Clinical Criteria for Sepsis. *JAMA* **315**, 762 (2016).
12. Fleischmann, C. *et al.* Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. *Am J Respir Crit Care Med* **193**, 259–272 (2016).

13. Stephen, A. H., Montoya, R. L. & Aluisio, A. R. Sepsis and Septic Shock in Low- and Middle-Income Countries. *Surg Infect (Larchmt)* **21**, 571–578 (2020).

14. Coopersmith, C. M. *et al.* Surviving sepsis campaign: research priorities for sepsis and septic shock. *Intensive Care Med* **44**, 1400–1426 (2018).

15. Sartelli, M. *et al.* Raising concerns about the Sepsis-3 definitions. *World Journal of Emergency Surgery* **13**, 1–9 (2018).

16. Rudd, K. E. *et al.* Association of the Quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) Score With Excess Hospital Mortality in Adults With Suspected Infection in Low- and Middle-Income Countries. *JAMA* **319**, 2202–2211 (2018).

17. Huson, M. A. M. *et al.* Application of the qSOFA score to predict mortality in patients with suspected infection in a resource-limited setting in Malawi. *Infection* **45**, 893–896 (2017).

18. Wright, S. W. *et al.* Enhanced bedside mortality prediction combining point-of-care lactate and the quick Sequential Organ Failure Assessment (qSOFA) score in patients hospitalised with suspected infection in southeast Asia: a cohort study. *Lancet Glob Health* **10**, e1281–e1288 (2022).

19. Siddiqui, E., Jokhio, A. A., Raheem, A., Waheed, S. & Hashmatullah, S. The Utility of Early Warning Score in Adults Presenting With Sepsis in the Emergency Department of a Low Resource Setting. *Cureus* **12**, (2020).

20. Rhodes, A. *et al.* Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med* **43**, 304–377 (2017).

21. NICE. *Sepsis: recognition, diagnosis and early management*. www.nice.org.uk/guidance/ng51 (2016).

22. Academy of Medical Royal Colleges. *Initial antimicrobial treatment of sepsis*. https://www.aomrc.org.uk/wp-content/uploads/2022/05/Statement_on_the_initial_antimicrobial_treatment_of_sepsis_0522.pdf (2022).

23. Daniels, R. *et al. The Sepsis Manual*. (United Kingdom Sepsis Trust, 2017).

24. Fleischmann-Struzek, C. *et al.* Incidence and mortality of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis. *Intensive Care Med* **46**, 1552–1562 (2020).

25. Rudd, K. E. *et al.* Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *The Lancet* **395**, 200–211 (2020).

26. Rudd, K. E. *et al.* The global burden of sepsis: barriers and potential solutions. *Crit Care* **22**, 232 (2018).

27. Finfer, S. & Machado, F. R. The Global Epidemiology of Sepsis. Does It Matter That We Know So Little? *Am J Respir Crit Care Med* **193**, 228–230 (2016).

28. World Health Organization. *Global report on the epidemiology and burden of sepsis: current evidence, identifying gaps and future directions*. (2020).

29. Shankar-Hari, M. & Rubenfeld, G. D. Understanding Long-Term Outcomes Following Sepsis: Implications and Challenges. *Curr Infect Dis Rep* **18**, (2016).

30. Lone, N. I. *et al.* Five-year mortality and hospital costs associated with surviving intensive care. *Am J Respir Crit Care Med* **194**, 198–208 (2016).

31. Hodgson, C. L., Walsh, T. S. & Lone, N. The long road home: are outcomes different for patients with sepsis? *Intensive Care Med* **44**, 1556–1557 (2018).

32. Cuthbertson, B. H. & Wunsch, H. Long-term outcomes after critical illness the best predictor of the future is the past. *Am J Respir Crit Care Med* **194**, 132–134 (2016).

33. Shankar-Hari, M. *et al.* Evidence for a causal link between sepsis and long-term mortality: A systematic review of epidemiologic studies. *Crit Care* **20**, 1–13 (2016).

34. Prescott, H. C., Osterholzer, J. J., Langa, K. M., Angus, D. C. & Iwashyna, T. J. Late mortality after sepsis: propensity matched cohort study. *BMJ* **353**, i2375 (2016).

35. Ou, S. M. *et al.* Long-term mortality and major adverse cardiovascular events in sepsis survivors a nationwide population-based study. *Am J Respir Crit Care Med* **194**, 209–217 (2016).

36. Thompson, K. *et al.* Health-related outcomes of critically ill patients with and without sepsis. *Intensive Care Med* **44**, 1249–1257 (2018).

37. Schmidt, K. *et al.* Sepsis survivors monitoring and coordination in outpatient health care (SMOOTH): study protocol for a randomized controlled trial. *Trials* **15**, 283 (2014).

38. Iwashyna, T. J., Ely, E. W., Smith, D. M. & Langa, K. M. Long-term Cognitive Impairment and Functional Disability Among Survivors of Severe Sepsis. *JAMA* **304**, 1787 (2010).

39. Cuthbertson, B. H. *et al.* Mortality and quality of life in the five years after severe sepsis. *Crit Care* **17**, 1–8 (2013).

40. Yende, S. *et al.* Risk of cardiovascular events in survivors of severe sepsis. *Am J Respir Crit Care Med* **189**, 1065–1074 (2014).

41. Garcia, M. A. *et al.* Association between Troponin I Levels during Sepsis and Postsepsis Cardiovascular Complications. *Am J Respir Crit Care Med* **204**, 557–565 (2021).

42. Yende, S., Iwashyna, T. J. & Angus, D. C. Interplay between sepsis and chronic health. *Trends Mol Med* **20**, 234–238 (2014).

43. Shankar-Hari, M. *et al.* Rate and risk factors for rehospitalisation in sepsis survivors: systematic review and meta-analysis. *Intensive Care Med* (2020) doi:10.1007/s00134-019-05908-3.

44. Shankar-Hari, M., Rubenfeld, G. D., Ferrando-Vivas, P., Harrison, D. A. & Rowan, K. Development, Validation, and Clinical Utility Assessment of a Prognostic Score for 1-Year Unplanned Rehospitalization or Death of Adult Sepsis Survivors. *JAMA Netw Open* **3**, e2013580 (2020).

45. Prescott, H. C., Langa, K. M. & Iwashyna, T. J. Readmission diagnoses after hospitalization for severe sepsis and other acute medical conditions. *JAMA - Journal of the American Medical Association* **313**, 1055–1057 (2015).

46. Prescott, H. C., Langa, K. M., Liu, V., Escobar, G. J. & Iwashyna, T. J. Increased 1-Year Healthcare Use in Survivors of Severe Sepsis. *Am J Respir Crit Care Med* **190**, 62–69 (2014).

47. Liu, V. *et al.* Hospital readmission and healthcare utilization following sepsis in community settings. *J Hosp Med* **9**, 502–7 (2014).

48. Lone, N. I. *et al.* Five-Year Mortality and Hospital Costs Associated with Surviving Intensive Care. *Am J Respir Crit Care Med* **194**, 198–208 (2016).

49. Shankar-Hari, M., Harrison, D. A., Ferrando-Vivas, P., Rubenfeld, G. D. & Rowan, K. Risk Factors at Index Hospitalization Associated With Longer-term Mortality in Adult Sepsis Survivors. *JAMA Netw Open* **2**, e194900 (2019).

50. Jones, T. K. *et al.* Post–Acute Care Use and Hospital Readmission after Sepsis. *Ann Am Thorac Soc* **12**, 904–913 (2015).

51. Goodwin, A. J., Rice, D. A., Simpson, K. N. & Ford, D. W. Frequency, Cost and Risk Factors of Readmissions among Severe Sepsis Survivors. *Crit Care Med* **43**, 738–746 (2015).

52. Lone, N. I. *et al.* Predicting risk of unplanned hospital readmission in survivors of critical illness: a population-level cohort study. *Thorax* thoraxjnl-2017-210822 (2018) doi:10.1136/thoraxjnl-2017-210822.

53. Henriksen, D. P. *et al.* Risk Factors for Hospitalization Due to Community-Acquired Sepsis – A Population-Based Case-Control Study. *PLoS One* **10**, e0124838 (2015).

54. Martin, G. S., Mannino, D. M. & Moss, M. The effect of age on the development and outcome of adult sepsis. *Crit Care Med* **34**, 15–21 (2006).

55. Wang, H. E. *et al.* Chronic Medical Conditions and Risk of Sepsis. *PLoS One* **7**, (2012).

56. Rezel-Potts, E. *et al.* Sepsis recording in primary care electronic health records, linked hospital episodes and mortality records: Population-based cohort study in England. *PLoS One* **15**, (2020).

57. Tavaré, A. & O'Flynn, N. Recognition, diagnosis, and early management of sepsis: NICE guideline. *Br J Gen Pract* **67**, 185–186 (2017).

58. Zador, Z., Landry, A., Cusimano, M. D. & Geifman, N. Multimorbidity states associated with higher mortality rates in organ dysfunction and sepsis: a data-driven analysis in critical care. *Crit Care* **23**, 247 (2019).

59. Novosad, S., Sapiano, M. & Grigg, C. Vital Signs: Epidemiology of Sepsis: Prevalence of Health Care Factors and Opportunities for Prevention. *Ann Emerg Med* **69**, 131–135 (2017).

60. Wang, H. E. *et al.* Derivation of novel risk prediction scores for community-acquired sepsis and severe sepsis. *Crit Care Med* **44**, 1285–1294 (2016).

61. Mahalingam, M., Moore, J. X., Donnelly, J. P., Safford, M. M. & Wang, H. E. Frailty Syndrome and Risk of Sepsis in the REasons for Geographic And Racial Differences in Stroke (REGARDS) Cohort. *J Intensive Care Med* **34**, 292–300 (2019).

62. Wang, H. E. *et al.* Inflammatory and endothelial activation biomarkers and risk of sepsis: A nested case-control study. *J Crit Care* **28**, 549–555 (2013).

63. Scicluna, B. P. *et al.* Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study. *Lancet Respir Med* **5**, 816–826 (2017).

64. Davenport, E. E. *et al.* Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study. *Lancet Respir Med* **4**, 259–271 (2016).

65. Wong, H. R. *et al.* Combining Prognostic and Predictive Enrichment Strategies to Identify Children With Septic Shock Responsive to Corticosteroids. *Crit Care Med* **44**, e1000-3 (2016).

66. DeMerle, K. M. *et al.* Sepsis Subclasses. *Crit Care Med* **Publish Ah**, (2021).

67. Leligdowicz, A. & Matthay, M. A. Heterogeneity in sepsis: new biological evidence with clinical applications. *Crit Care* **23**, (2019).

68. Adelman, M. W. *et al.* The gut microbiome's role in the development, maintenance, and outcomes of sepsis. *Crit Care* **24**, 1–10 (2020).

69. Kullberg, R. F. J., Wiersinga, W. J. & Haak, B. W. Gut microbiota and sepsis: From pathogenesis to novel treatments. *Curr Opin Gastroenterol* **37**, 578–585 (2021).

70. Prescott, H. C., Dickson, R. P., Rogers, M. A. M., Langa, K. M. & Iwashyna, T. J. Hospitalization type and subsequent severe sepsis. *Am J Respir Crit Care Med* **192**, 581–588 (2015).

71. Baggs, J. *et al.* Risk of Subsequent Sepsis within 90 Days of a Previous Hospital Stay by Type of Antibiotic Exposure. *Clin Infect Dis* **66**, 1004 (2018).

72. Wan, Y.-D. *et al.* Gut Microbiota Disruption in Septic Shock Patients: A Pilot Study. doi:10.12659/MSM.911768.

73. Melzer, M. & Welch, C. Does the presence of a urinary catheter predict severe sepsis in a bacteraemic cohort? *Journal of Hospital Infection* **95**, 376–382 (2017).

74. Prescott, H. C., Carmichael, A. G., Langa, K. M., Gonzalez, R. & Iwashyna, T. J. Paths into sepsis: Trajectories of presepsis healthcare use. *Ann Am Thorac Soc* **16**, 116–123 (2019).

75. Buchman, T. G. *et al.* Sepsis among Medicare beneficiaries: 2. The trajectories of sepsis, 2012-2018. *Crit Care Med* 289–301 (2020) doi:10.1097/CCM.0000000000004226.

76. Jones, S. L. *et al.* Outcomes and resource use of sepsis-associated stays by presence on admission, severity, and hospital type. *Med Care* **54**, 303–310 (2016).

77. Page, D. B., Donnelly, J. P. & Wang, H. E. Community-, Healthcare-, and Hospital-Acquired Severe Sepsis Hospitalizations in the University HealthSystem Consortium. *Crit Care Med* **43**, 1945–51 (2015).

78. Adrie, C. *et al.* Epidemiology and economic evaluation of severe sepsis in France: age, severity, infection site, and place of acquisition (community, hospital, or intensive care unit) as determinants of workload and cost. *J Crit Care* **20**, 46–58 (2005).

79. Sousa, C., Brandão, M., Ribeiro, O. & Cardoso, T. Community-Acquired Severe Sepsis: A Prospective Cohort Study. *Open Journal of Internal Medicine* **05**, 37–49 (2015).

80. Shah, A. D. *et al.* Descriptors of Sepsis Using the Sepsis-3 Criteria: A Cohort Study in Critical Care Units Within the U.K. National Institute for Health Research Critical Care Health Informatics Collaborative*. *Crit Care Med* **49**, 1883–1894 (2021).

81. Tonai, M. *et al.* Hospital-onset sepsis and community-onset sepsis in critical care units in Japan: a retrospective cohort study based on a Japanese administrative claims database. *Crit Care* **26**, 1–9 (2022).

82. Rothman, M. *et al.* Sepsis as 2 problems: Identifying sepsis at admission and predicting onset in the hospital using an electronic medical record–based acuity score. *J Crit Care* **38**, 237–244 (2017).

83. Sakr, Y. *et al.* Sepsis in Intensive Care Unit Patients: Worldwide data from the ICON audit. *Open Forum Infect Dis* **5**, (2018).

84. Westphal, G. A. *et al.* Characteristics and outcomes of patients with community-acquired and hospital-acquired sepsis. *Rev Bras Ter Intensiva* **31**, 71–78 (2019).

85. Padro, T. *et al.* Admission characteristics predictive of in-hospital death from hospital-acquired sepsis: A comparison to community-acquired sepsis. *J Crit Care* **51**, 145–148 (2019).

86. Pierrakos, C. & Vincent, J.-L. Sepsis biomarkers: a review. *Crit Care* **14**, R15 (2010).

87. Rhee, C. *et al.* Diagnosing sepsis is subjective and highly variable: a survey of intensivists using case vignettes. *Crit Care* **20**, 89 (2016).

88. Paul, M. *et al.* Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. *Antimicrob Agents Chemother* **54**, 4851–4863 (2010).

89. Abe, T. *et al.* In-hospital mortality associated with the misdiagnosis or unidentified site of infection at admission. *Crit Care* **23**, 202 (2019).

90. Scott, L. J. *et al.* Distributions of the National Early Warning Score (NEWS) across a healthcare system following a large-scale roll-out. *Emerg Med J* **36**, 287–292 (2019).

91. Faisal, M. *et al.* Computer-aided National Early Warning Score to predict the risk of sepsis following emergency medical admission to hospital: a model development and external validation study. *Can Med Assoc J* **191**, E382–E389 (2019).

92. Faisal, M. *et al.* Development and external validation of an automated computer-aided risk score for predicting sepsis in emergency medical admissions using the patient's first electronically recorded vital signs and blood test results. *Crit Care Med* **46**, 612–618 (2018).

93. Churpek, M. M. *et al.* Quick Sepsis-related Organ Failure Assessment, Systemic Inflammatory Response Syndrome, and Early Warning Scores for Detecting Clinical Deterioration in Infected Patients outside the Intensive Care Unit. *Am J Respir Crit Care Med* **195**, 906–911 (2017).

94. Sims, C. R., Nguyen, T. C. & Mayeux, P. R. Could Biomarkers Direct Therapy for the Septic Patient? *Journal of Pharmacology and Experimental Therapeutics* **357**, 228–239 (2016).

95. Klein Klouwenberg, P. M. C. *et al.* Likelihood of infection in patients with presumed sepsis at the time of intensive care unit admission: a cohort study. *Crit Care* **19**, 319 (2015).

96. Daniels, R., Nutbeam, T., Mcnamara, G. & Galvin, C. The sepsis six and the severe sepsis resuscitation bundle: a prospective observational cohort study. *Emergency Medicine Journal* **28**, 507–512 (2011).

97. Levy, M. M., Evans, L. E. & Rhodes, A. The Surviving Sepsis Campaign Bundle: 2018 Update. *Crit Care Med* **46**, 997–1000 (2018).

98. Cherukuri, L., Gewirtz, G., Osea, K. & Tayek, J. A. Vitamin A treatment for severe sepsis in humans; a prospective randomized double blind placebo-controlled clinical trial. *Clin Nutr ESPEN* **29**, 49–51 (2019).

99. Pertzov, B. *et al.* Hydroxymethylglutaryl-CoA reductase inhibitors (statins) for the treatment of sepsis in adults – a systematic review and meta-analysis. *Clinical Microbiology and Infection* **25**, 280–289 (2019).

100. Zhang, H., Feng, Y. & Yao, Y. Potential therapy strategy: targeting mitochondrial dysfunction in sepsis. *Mil Med Res* **5**, 41 (2018).

101. Panacek, E. A. *et al.* Efficacy and safety of the monoclonal anti-tumor necrosis factor antibody F(ab')2 fragment afelimomab in patients with severe sepsis and elevated interleukin-6 levels. *Crit Care Med* **32**, 2173–82 (2004).

102. Evans, L. *et al.* Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. *Crit Care Med* **49**, E1063–E1143 (2021).

103. Ferrer, R. *et al.* Empiric Antibiotic Treatment Reduces Mortality in Severe Sepsis and Septic Shock From the First Hour: Results From a Guideline-Based Performance Improvement Program*. *Crit Care Med* **42**, 1749–1755 (2014).

104. Dryden, M., Johnson, A. P., Ashiru-Oredope, D. & Sharland, M. Using antibiotics responsibly: right drug, right time, right dose, right duration. *Journal of Antimicrobial Chemotherapy* **66**, 2441–2443 (2011).

105. Gaieski, D. F. *et al.* Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. *Crit Care Med* **38**, 1045–1053 (2010).

106. Liu, V. X. *et al.* The Timing of Early Antibiotics and Hospital Mortality in Sepsis. *Am J Respir Crit Care Med* **196**, 856–863 (2017).

107. Im, Y. *et al.* Time-to-antibiotics and clinical outcomes in patients with sepsis and septic shock: a prospective nationwide multicenter cohort study. *Crit Care* **26**, 1–10 (2022).

108. de Groot, B. *et al.* The association between time to antibiotics and relevant clinical outcomes in emergency department patients with various stages of sepsis: A prospective multi-center study. *Crit Care* **19**, 1–12 (2015).

109. Sterling, S. A., Miller, W. R., Pryor, J., Puskarich, M. A. & Jones, A. E. The Impact of Timing of Antibiotics on Outcomes in Severe Sepsis and Septic Shock: A Systematic Review and Meta-Analysis. *Crit Care Med* **43**, 1907–15 (2015).

110. Johnston, A. N. B. *et al.* Effect of Immediate Administration of Antibiotics in Patients With Sepsis in Tertiary Care: A Systematic Review and Meta-analysis. *Clin Ther* **39**, 190-202.e6 (2017).

111. Sherwin, R., Winters, M. E., Vilke, G. M. & Wardi, G. Does Early and Appropriate Antibiotic Administration Improve Mortality in Emergency Department Patients with Severe Sepsis or Septic Shock? *Journal of Emergency Medicine* **53**, 588–595 (2017).

112. Klompas, M., Calandra, T. & Singer, M. Antibiotics for Sepsis—Finding the Equilibrium. *JAMA* **320**, 1433 (2018).

113. Singer, M. Antibiotics for sepsis: Does each hour really count, or is it incestuous amplification? *Am J Respir Crit Care Med* **196**, 800–802 (2017).

114. Kalil, A. C. & Timsit, J. F. Less is more : critically ill status is not a carte blanche for unlimited antibiotic use. *Intensive Care Med* (2020) doi:10.1007/s00134-020-06260-7.

115. Llewelyn, M. J. *et al.* The antibiotic course has had its day. *BMJ* **358**, j3418 (2017).

116. Schuetz, P. *et al.* Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis. *Lancet Infect Dis* **18**, 95–107 (2018).

117. Huang, D. T. *et al.* Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection. *New England Journal of Medicine* **379**, 236–249 (2018).

118. de Jong, E. *et al.* Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. *Lancet Infect Dis* **16**, 819–827 (2016).

119. Uranga, A. *et al.* Duration of Antibiotic Treatment in Community-Acquired Pneumonia. *JAMA Intern Med* **176**, 1257 (2016).

120. Spellberg, B. The New Antibiotic Mantra—"Shorter Is Better". *JAMA Intern Med* **176**, 1254 (2016).

121. Tabah, A. *et al.* Antimicrobial de-escalation in critically ill patients: a position statement from a task force of the European Society of Intensive Care Medicine (ESICM) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Critically Ill Patient. *Intensive Care Med* **46**, 245–265 (2020).

122. Hellyer, T. P., Mantle, T., Mcmullan, R. & Dark, P. How to optimise duration of antibiotic treatment in patients with sepsis? *BMJ* **371**, 11–13 (2020).

123. Kumar, A. *et al.* Initiation of Inappropriate Antimicrobial Therapy Results in a Fivefold Reduction of Survival in Human Septic Shock. *Chest* **136**, 1237–1248 (2009).

124. Suberviola Cañas, B. *et al.* Effects of antibiotic administration delay and inadequacy upon the survival of septic shock patients. *Medicina Intensiva (English Edition)* **39**, 459–466 (2015).

125. Micek, S. T., Hampton, N. & Kollef, M. Risk Factors and Outcomes for Ineffective Empiric Treatment of Sepsis Caused by Gram-Negative Pathogens: Stratification by Onset of Infection. *Antimicrob Agents Chemother* **62**, e01577-17 (2018).

126. Zilberberg, M. D., Shorr, A. F., Micek, S. T., Vazquez-Guillamet, C. & Kollef, M. H. Multi-drug resistance, inappropriate initial antibiotic therapy and mortality in Gram-negative severe sepsis and septic shock: a retrospective cohort study. *Crit Care* **18**, 596 (2014).

127. Martínez, M. L., Plata-Menchaca, E. P., Ruiz-Rodríguez, J. C. & Ferrer, R. An approach to antibiotic treatment in patients with sepsis. *J Thorac Dis* **12**, 1007–1021 (2020).

128. Smith, D. R. M. *et al.* Defining the appropriateness and inappropriateness of antibiotic prescribing in primary care. *Journal of Antimicrobial Chemotherapy* **73**, ii11–ii18 (2018).

129. Smieszek, T. *et al.* Potential for reducing inappropriate antibiotic prescribing in English primary care. *Journal of Antimicrobial Chemotherapy* **73**, ii36–ii43 (2018).

130. Nowakowska, M. *et al.* Antibiotic choice in UK general practice: Rates and drivers of potentially inappropriate antibiotic prescribing. *Journal of Antimicrobial Chemotherapy* **74**, 3371–3378 (2019).

131. van Bodegraven, B. *et al.* Infection-related complications after common infection in association with new antibiotic prescribing in primary care: retrospective cohort study using linked electronic health records. *BMJ Open* **11**, e041218 (2021).

132. Gulliford, M. C. *et al.* Serious bacterial infections and antibiotic prescribing in primary care: cohort study using electronic health records in the UK. *BMJ Open* **10**, e036975 (2020).

133. Van Staa, T. P. *et al.* The effectiveness of frequent antibiotic use in reducing the risk of infection-related hospital admissions: Results from two large population-based cohorts. *BMC Med* **18**, 1–11 (2020).

134. Gharbi, M. *et al.* Antibiotic management of urinary tract infection in elderly patients in primary care and its association with bloodstream infections and all cause mortality: population based cohort study. *BMJ* **364**, l525 (2019).

135. Little, P. *et al.* Antibiotic prescription strategies and adverse outcome for uncomplicated lower respiratory tract infections: prospective cough complication cohort (3C) study. *BMJ* **357**, (2017).

136. Mistry, C. *et al.* Development and validation of a multivariable prediction model for infection-related complications in patients with common infections in UK primary care and the extent of risk-based prescribing of antibiotics. *BMC Med* **18**, 1–13 (2020).

137. Gulliford, M. C. *et al.* Probability of sepsis after infection consultations in primary care in the United Kingdom in 2002-2017: Population-based cohort study and decision analytic model. *PLoS Med* **17**, e1003202 (2020).

138. Ventola, C. L. The antibiotic resistance crisis: part 1: causes and threats. *P & T : A peer-reviewed journal for formulary management (2015)* **40**, 277–83 (2015).

139. O'Neill, J. *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*. https://amr-review.org/sites/default/files/160525_Final paper_with cover.pdf (2016) doi:10.1016/j.jpha.2015.11.005.

140. WHO. *Antimicrobial resistance. Global report on surveillance*. *World Health Organization* vol. 61 (2014).

141. Cassini, A. *et al.* Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis* **19**, 56–66 (2019).

142. Shallcross, L. J. & Davies, S. C. Antibiotic overuse: A key driver of antimicrobial resistance. *British Journal of General Practice* vol. 64 604–605 Preprint at https://doi.org/10.3399/bjgp14X682561 (2014).

143. Costelloe, C., Metcalfe, C., Lovering, A., Mant, D. & Hay, A. D. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: Systematic review and meta-analysis. *BMJ (Online)* **340**, 1120 (2010).

144. Department of Health & Social Care & Department of Environment Food & Rural Affairs. *Tackling antimicrobial resistance 2019-2024: Global and Public Health Group Emergency Preparedness and Health Protection Policy Directorate*. (2019).

145. Sun, X. & Gulliford, M. C. Reducing antibiotic prescribing in primary care in England from 2014 to 2017: Population-based cohort study. *BMJ Open* **9**, (2019).

146. Balinskaite, V., Johnson, A. P., Holmes, A. & Aylin, P. The Impact of a National Antimicrobial Stewardship Program on Antibiotic Prescribing in Primary Care: An Interrupted Time Series Analysis. *Clinical Infectious Diseases* **69**, 227–232 (2019).

147. Balinskaite, V., Bou-Antoun, S., Johnson, A. P., Holmes, A. & Aylin, P. An assessment of potential unintended consequences following a national antimicrobial stewardship program in England: An interrupted time series analysis. *Clinical Infectious Diseases* **69**, 233–242 (2019).

148. Anyanwu, P. E. *et al.* Investigating the mechanism of impact and differential effect of the Quality Premium scheme on antibiotic prescribing in England: a longitudinal study. *BJGP Open* **4**, (2020).

149. van Staa, T. P. *et al.* Comparing antibiotic prescribing between clinicians in UK primary care: an analysis in a cohort study of eight different measures of antibiotic prescribing. *BMJ Qual Saf* **0**, bmjqs-2020-012108 (2022).

150. Boiko, O., Burgess, C., Fox, R., Ashworth, M. & Gulliford, M. C. Risks of use and non-use of antibiotics in primary care: qualitative study of prescribers' views. *BMJ Open* **10**, e038851 (2020).

151. Boiko, O., Gulliford, M. C. & Burgess, C. Revisiting patient expectations and experiences of antibiotics in an era of antimicrobial resistance: Qualitative study. *Health Expect* **23**, 1250–1258 (2020).

152. Angus, D. C. *et al.* Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* **29**, 1303–1310 (2001).

153. Martin, G. S., Mannino, D. M., Eaton, S. & Moss, M. The Epidemiology of Sepsis in the United States from 1979 through 2000. *New England Journal of Medicine* **348**, 1546–1554 (2003).

154. Wilhelms, S. B., Huss, F. R., Granath, G. & Sjöberg, F. Assessment of incidence of severe sepsis in Sweden using different ways of abstracting International Classification of Diseases codes: Difficulties with methods and interpretation of results. *Crit Care Med* **38**, 1442–1449 (2010).

155. Mariansdatter, S. E., Eiset, A. H., Søgaard, K. K. & Christiansen, C. F. Differences in reported sepsis incidence according to study design: a literature review. *BMC Med Res Methodol* **16**, 1–13 (2016).

156. Johnson, A. E. W. *et al.* A Comparative Analysis of Sepsis Identification Methods in an Electronic Database. *Crit Care Med* **46**, 1 (2018).

157. Wang, H. E. *et al.* Discharge diagnoses versus medical record review in the identification of community-acquired sepsis. *Crit Care* **19**, 42 (2015).

158. Enoch, D. A. *et al.* Risk of complications and mortality following recurrent and non-recurrent Clostridioides difficile infection: a retrospective observational database study in England. *Journal of Hospital Infection* **106**, 793–803 (2020).

159. Panacek, E. A. *et al.* Efficacy and safety of the monoclonal anti-tumor necrosis factor antibody F(ab′) 2 fragment afelimomab in patients with severe sepsis and elevated interleukin-6 levels. *Crit Care Med* **32**, 2173–2182 (2004).

160. Marshall, J. C. Why have clinical trials in sepsis failed? *Trends Mol Med* **20**, 195–203 (2014).

161. Prescott, H. C., Calfee, C. S., Taylor Thompson, B., Angus, D. C. & Liu, V. X. Toward smarter lumping and smarter splitting: Rethinking strategies for sepsis and acute respiratory distress syndrome clinical trial design. *Am J Respir Crit Care Med* **194**, 147–155 (2016).

162. Zhang, Z., Zhang, G., Goyal, H., Mo, L. & Hong, Y. Identification of subclasses of sepsis that showed different clinical outcomes and responses to amount of fluid resuscitation: a latent profile analysis. *Crit Care* **22**, 347 (2018).

163. New, J. P., Leather, D., Bakerly, N. D., McCrae, J. & Gibson, J. M. Putting patients in control of data from electronic health records. *BMJ* **360**, j5554 (2018).

164. National Health Service. *The NHS Long Term Plan*. www.longtermplan.nhs.uk (2019) doi:10.38192/12.1.4.

165. Johnson, A. E. W. *et al.* Machine Learning and Decision Support in Critical Care. *Proceedings of the IEEE* **104**, 444–466 (2016).

166. Maslove, D. M., Dubin, J. A., Shrivats, A. & Lee, J. Errors, Omissions, and Outliers in Hourly Vital Signs Measurements in Intensive Care. *Crit Care Med* **44**, e1021–e1030 (2016).

167. Jones, K. H., Ford, D. V., Thompson, S. & Lyons, R. A. A Profile of the SAIL Databank on the UK Secure Research Platform. *Int J Popul Data Sci* **4**, (2019).

168. Curtis, H. J. *et al.* OpenSAFELY NHS Service Restoration Observatory 1: primary care clinical activity in England during the first wave of COVID-19. *British Journal of General Practice* **72**, e63–e74 (2022).

169. Andrews, C. D. *et al.* OpenSAFELY: Representativeness of Electronic Health Record platform OpenSAFELY-TPP data compared to the population of England. *medRxiv* 2022.06.23.22276802 (2022) doi:10.1101/2022.06.23.22276802.

170. OpenSAFELY. About OpenSAFELY. https://www.opensafely.org/about/.

171. Herbert, A., Wijlaars, L., Zylbersztejn, A., Cromwell, D. & Hardelid, P. Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). *Int J Epidemiol* **46**, 1093 (2017).

172. Harrison, D. A., Brady, A. R. & Rowan, K. Case mix, outcome and length of stay for admissions to adult, general critical care units in England, Wales and Northern Ireland: The Intensive Care National Audit and Research Centre Case Mix Programme Database. *Crit Care* **9**, 1–13 (2004).

173. Scottish Intensive Care Society Audit Group. *Audit of critical care in Scotland 2022: Reporting on 2021*. (2022).

174. Harrison, D. A., Parry, G. J., Carpenter, J. R., Short, A. & Rowan, K. A new risk prediction model for critical care: The Intensive Care National Audit & Research Centre (ICNARC) model. *Crit Care Med* **35**, 1091–1098 (2007).

175. Harrison, D. A., Brady, A. R., Parry, G. J., Carpenter, J. R. & Rowan, K. Recalibration of risk prediction models in a large multicenter cohort of admissions to adult, general critical care units in the United Kingdom. *Crit Care Med* **34**, 1378–1388 (2006).

176. Ferrando-Vivas, P., Jones, A., Rowan, K. M. & Harrison, D. A. Development and validation of the new ICNARC model for prediction of acute hospital mortality in adult critical care. *J Crit Care* **38**, 335–339 (2017).

177. Johnson, A. *et al.* MIMIC-III, a freely accessible critical care database. *Sci Data* **3**, 1–9 (2016).

178. Thoral, P. J. *et al.* Sharing ICU Patient Data Responsibly Under the Society of Critical Care Medicine/European Society of Intensive Care Medicine Joint Data Science Collaboration: The Amsterdam University Medical Centers Database (AmsterdamUMCdb) Example*. *Crit Care Med* **49**, e563 (2021).

179. Sauer, C. M. *et al.* Systematic Review and Comparison of Publicly Available ICU Data Sets—A Decision Guide for Clinicians and Data Scientists. *Crit Care Med* **50**, e581–e588 (2022).

180. Carter, P., Laurie, G. T. & Dixon-Woods, M. The social licence for research: why care.data ran into trouble. *J Med Ethics* **41**, 404–409 (2015).

181. Harris, S. *et al.* Critical Care Health Informatics Collaborative (CCHIC): Data, tools and methods for reproducible research: A multi-centre UK intensive care database. *Int J Med Inform* **112**, 82–89 (2018).

182. Shi, S. *et al.* Critical care data processing tools. *The Journal of Open Source Software* **2**, 513 (2017).

183. Griffiths, R. *et al.* INTEGRATE: A methodology to facilitate critical care research using multiple, linked electronic health records at population scale. *Int J Popul Data Sci* **7**, (2022).

184. Schenck, E. J. *et al.* Critical carE Database for Advanced Research (CEDAR): An automated method to support intensive care units with electronic health record data. *J Biomed Inform* **118**, 103789 (2021).

185. Carra, G., Salluh, J. I. F., da Silva Ramos, F. J. & Meyfroidt, G. Data-driven ICU management: Using Big Data and algorithms to improve outcomes. *J Crit Care* **60**, 300–304 (2020).

186. Johnson, A. E. W. *et al.* Machine Learning and Decision Support in Critical Care. *Proceedings of the IEEE* **104**, 444–466 (2016).

187. Sanchez-Pinto, L. N., Luo, Y. & Churpek, M. M. Big Data and Data Science in Critical Care. *Chest* **154**, 1239–1248 (2018).

188. Shah, F. A. *et al.* A Research Agenda for Precision Medicine in Sepsis and Acute Respiratory Distress Syndrome: An Official American Thoracic Society Research Statement. *https://doi-org.manchester.idm.oclc.org/10.1164/rccm.202108-1908ST* **204**, 891–901 (2021).

189. Seymour, C. W. *et al.* Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* **315**, 762–774 (2016).

190. Knox, D. B., Lanspa, M. J., Kuttler, K. G., Brewer, S. C. & Brown, S. M. Phenotypic clusters within sepsis-associated multiple organ dysfunction syndrome. *Intensive Care Med* **41**, 814–822 (2015).

191. Tarabichi, Y. *et al.* Improving Timeliness of Antibiotic Administration Using a Provider and Pharmacist Facing Sepsis Early Warning System in the Emergency Department Setting. *Crit Care Med* **Publish Ah**, 1–10 (2021).

192. Tartof, S. Y. *et al.* Development and Assessment of Risk Scores for Carbapenem and Extensive β-Lactam Resistance Among Adult Hospitalized Patients With Pseudomonas aeruginosa Infection. *JAMA Netw Open* **1**, e183927–e183927 (2018).

193. Komorowski, M., Celi, L. A., Badawi, O., Gordon, A. C. & Faisal, A. A. The Artificial Intelligence Clinician learns optimal treatment strategies for sepsis in intensive care. *Nat Med* 1 (2018) doi:10.1038/s41591-018-0213-5.

194. de Oliveira, H. *et al.* “Bow-tie” optimal pathway discovery analysis of sepsis hospital admissions using the Hospital Episode Statistics database in England. *JAMIA Open* **3**, 439–448 (2020).

Chapter 2 – Aims & Objectives

There were three main aims of this thesis, looking at the role and use of antibiotics in three stages of the sepsis patient's pathway:

1. To use linked primary and secondary care EHR data to explore the risk factors associated with developing sepsis, including previous antibiotic use, in order to identify people most at risk. Specific objectives were to:
    1. identify demographic and comorbid factors associated with developing sepsis
    2. evaluate whether these risk factors differ between patients who develop sepsis in the community or in hospital
    3. evaluate whether history of regular antibiotic use associated with an increased risk of developing sepsis
2. To use EHR data to estimate the burden of sepsis patients in terms of antibiotic use during a hospital admission and relate it to short-term mortality. Specific objectives were to:
    1. describe the types of antimicrobials, and how much of these, sepsis patients are exposed to
    2. evaluate the short-term mortality outcomes of sepsis patients
    3. evaluate whether patients with higher antimicrobial exposure have higher short-term survival rates
3. To use linked primary and secondary care EHR data to investigate the long-term outcomes in sepsis survivors and to evaluate differences between community- and hospital-acquired sepsis. Specific objectives were to:
    1. determine hospital readmission and mortality rates, and their predictors, following a sepsis episode
    2. determine whether patients develop additional comorbidities after a sepsis episode
    3. evaluate whether patients who survive a sepsis episode have increased incidence of common infections and antibiotic prescribing in primary care

Each aim is addressed in a separate study and presented in this thesis in three chapters. The studies for aims one and three (chapter 4 and chapter 6) use linked primary and secondary care data from an English data source, whilst aim two is addressed in a study using a US ICU database (chapter 5).

As I am presenting this thesis in a journal-style format with distinct manuscripts for each of the three studies, in the following chapter (chapter 3) I will provide additional detail around the data sources and methods I have use to address the above aims.

Chapter 3 – Methods

3.1 Data sources

For the studies in this thesis I have used data from CPRD linked with HES, and MIMIC-III. Although they were mentioned briefly in the first chapter there are more details here.

3.1.1 Clinical Practice Research Datalink (CPRD) & Hospital Episode Statistics (HES)

CPRD is a source of de-identified UK primary care data, consisting of two databases from general practices (GPs) using two different electronic health record systems. CPRD Gold collects data from practices using Vision software, and covers approximately 11 million current and historic patients, around 4.5% of the current UK population. The number of GP's using Vision software has declined meaning there are fewer active patients in the database[1]. CPRD Aurum gathers data from GPs using EMIS software and contains data from a total of around 45 million current and historic patients, and approximately 13% of the current English population[2]. Both databases have been shown to be broadly representative of the UK in terms of age, sex and ethnicity, although they do vary geographically in the areas they cover[1,2]. As well as whole practices leaving the CPRD registration individual patients can also choose to opt-out of letting their personal data be shared.

The data available in CPRD consists of coded information around diagnoses, tests performed, prescriptions, referrals as well as clinical observations recorded by the GP. It can also include information relayed back to a GP from other healthcare providers (i.e. hospitals) and manually entered retrospectively into a patient's record. Any information recorded in patient records by a clinician as free text is not available to researchers, as this is potentially identifiable data. The coding systems used by the practices contributing to Gold and Aurum does differ. The Gold data is coded mainly using READ codes, whilst Aurum practices use a combination of READ, SNOMED CT and EMIS Web codes[1,2]. This does mean that researchers need to generate different code lists when working with both datasets. The structure of the datasets also differs, so the extraction of data must be done separately for each database. The data is organised in different tables, so there are separate tables for a consultation, diagnoses & symptoms, prescriptions, test results etc. Each patient has a unique ID (not NHS number) and each visit or consultation will have a distinct visit ID assigned to it. These unique ID's can be used to extract necessary data from each table. Once the data was extracted and cleaned for the separate cohorts, the data was amalgamated. All analysis was carried out on the separate

cohorts and the combined cohort. The results reported in the manuscripts are for the combined cohort, the results from the separate cohorts can be found in the supplementary materials.

Through CPRD it is possible to link GP data with other sources, including Hospital Episode Statistics (HES) data, Office for National Statistics (ONS) mortality data, and deprivation measures at both practice and patient level such as Index of Multiple Deprivation (IMD) and Townsend Deprivation Index. It is also possible to link with other registries including the National Cancer Registration and Analysis Service and a Mental Health Dataset.

HES data is collected by NHS Digital and covers all hospital admissions in England only, and has separate datasets covering admitted patient care, outpatient care, accident & emergency, diagnostic imaging and some critical care[3]. The method of linking patients HES data to their primary care records is done through a deterministic stepwise approach, using a combination of NHS number, gender, date of birth, and postcode. More details can be found in the paper by Padmanaban et al[4], around 96% of patients are acceptable for linkage. Additionally, not all CPRD practices have data sharing agreements with HES, so it is not possible to link all secondary care data to CPRD data. Overall, for the linkage set we used (set 20) there were 82% of patients in Aurum and 80% of Gold patients who were eligible for linkage with HES.

The data recorded in HES includes diagnostic details (ICD-10 codes), date and time of admission & discharge, type of admission, procedures (OPCS codes) and destination on discharge amongst others. It does not include any clinical observations or measurements, tests performed or drugs prescribed. The data is coded by clinical coders from discharge summaries, and there is some variation in how data is coded. An advantage of HES, however, is that it covers all hospitals in England and has been collecting linkable data since 1997/1998 so it is possible to follow patients up over a long period of time[3]. There are some data in HES around patient stays in critical care, either in an intensive care unit (ICU) or high dependency unit (HDU), however this has only been available from 2008/2009. In the critical care dataset there are details of the amount, duration and type of organ support required by patients. ONS mortality data covers deaths from England and Wales and as well as the date of death it also gives details of causes of deaths, coded using ICD-10 codes.

For my studies the main advantage of using this data source is that I could use the hospital admissions data to identify patients with sepsis, which is where most sepsis patients will be treated, but link that to GP data to get information around their health pre- and post- sepsis. Whilst sepsis is recorded in GP practices it is usually either done retrospectively after a hospital admission or if a GP suspects sepsis, but they may not actually have it. A study using CPRD Gold compared a cohort of patients identified in GP records with a cohort of patients

hospitalised with sepsis and found there were not many patients who had a record of sepsis in both[5].

In the studies using CPRD I have used a matched case-control design and have also divided the cohort into two subgroups, based on whether they were admitted to hospital with sepsis (community-acquired) or developed sepsis during a hospital admission for a different reason (hospital-acquired, episode started 2 days after hospital admission). The linked datasets also meant we could identify separate control groups for the two subgroups. For the community-acquired sepsis cases I identified population-based controls from the GP data, whereas for the hospital-acquired sepsis cases I could use the HES data to identify patients with non-sepsis admissions. This is a major strength of both of these studies, as there are few in the literature that differentiate between community- and hospital-acquired sepsis, and which use control groups.

To gain access to CPRD data a protocol (ISAC protocol) has to be written and approved, with details of the analysis plan and data needed. The approved protocol can be found in the appendices of this thesis, however, there are some differences in the approved protocol and the analyses carried out. The main change was in the age of the cohort. Originally I intended on using a cohort of any age and conducting analyses separately in adults and children below 18 years of age. However, due to reasons which are discussed further on in this chapter the analysis was carried out in a cohort of patients over the age of 65 only. In the protocol I stated the definition of community- and hospital-acquired sepsis would be 48 hours, however, the data provided in HES records only provides date stamps, not time stamps. The cut-off point we used therefore was changed to two full calendar days. Additional changes in patient selection included increasing the time period from 2018 – 2020 as the data extraction was not done until December 2020 and excluding patients with a GP record of sepsis within 2 weeks of their hospital sepsis admission, not 6 weeks.

In terms of the analysis I did not include sepsis specific mortality or readmission rates, nor did I assess the critical care length of stay outcome as this data was not available in HES for the full study period. I also did not calculate the risk ratio for sepsis in relation to antibiotic prescribing and I used the missing indicator method in the analyses rather than multiple imputation. There were additional deviations in the covariates I used, including not calculating the Charlson prescription score, not using details of surgeries or procedures and not performing stepwise variable selection to select the final variables to include in the models.

3.1.2 Medical Information Mart for Intensive Care-III (MIMIC-III)

MIMIC-III is a database of electronic health records from patients treated in the ICUs of a single hospital in Boston, USA. There are anonymised details of over 53,000 ICU admissions of over 38,000 patients between 2001 and 2012. Compared to CPRD and HES data, MIMIC-III offered a much more comprehensive look at what happened to patients during their hospital admission for sepsis. There was a huge amount of data available around laboratory tests, diagnoses, procedures, drugs and fluids administered and clinical measurements from throughout their ICU stay. For each patient admission there is a mean of 4,579 date and time-stamped charted observations and 380 laboratory measurements[6]. There was therefore a large advantage to this dataset, both in terms of being able to identify patients with sepsis (more details below) and being able to understand how they have been treated.

The data within MIMIC-III is collected from two different EHR systems. CareVue was used for the years 2001-2008 and MetaVision was used from 2008 onwards. The majority of the data collected does not differ between the two systems, and so some of the data had been merged, however there are a couple of areas where there are differences, and data is in separate tables. These differences mean that researchers could be limited to patients from either of those two time periods, depending on their research question. For my study I was interested in data around prescriptions of antibiotics, which was only available in the MetaVision system, meaning I was restricted to sepsis patients treated between 2008 and 2012 only.

3.2 Patient identification

3.2.1 CPRD & HES

For the studies using CPRD and HES data, the only way to identify sepsis was using International Classification of Disease (ICD) codes. HES data uses the tenth version, which does offer a more comprehensive list of codes related to sepsis than ICD-9. It would have been possible to use either the Martin or Angus criteria (discussed in the literature review) to identify patients through CPRD, however because of the way the data is extracted it was more straightforward to use a more explicit code list, rather than combinations of codes. I did speak with a clinical coder at the Northern Care Alliance NHS Foundation Trust to compile the list of relevant codes to use (see supplementary material). As mentioned in the literature review, this method of identifying sepsis has the potential of a smaller cohort, with a more severe condition.

Each admission within HES has a primary diagnostic ICD-10 code, and additional codes available for the episodes of care that make up the patient's admission. I looked for patients who had a sepsis code at any point in their admission, not just as their primary diagnosis. In order to identify patients with community-acquired sepsis and hospital-acquired sepsis I looked at patients with an episode of care within an admission that had a code for sepsis, where that episode had started two calendar days after their hospital admission date, and there was no sepsis code in the initial episode on admission to the hospital.

I also needed to exclude patients who had any record of sepsis in their GP records. Primary care data is recorded using READ codes, not ICD codes, so it was not possible to us exactly the same set of codes to identify sepsis in GP record data.

3.2.2 MIMIC-III

With the MIMIC-III data it was possible to use a few different methods of identifying sepsis and compare the cohorts. The coding system used in MIMIC-III was ICD-9, which only has codes for sepsis, severe sepsis and septic shock. It was possible here to apply both the Martin and Angus code criteria, to pick up patients who had a code for infection in combination with a code for organ dysfunction. A slight issue with these criteria is that there were no time stamps available for the codes, they were all coded at the end of their hospital admission. This means it is not possible to know whether the infection and organ dysfunction actually occurred concurrently. The main advantage of using the MIMIC-III data was that because of the availability of time-stamped clinical observations data it was possible to identify patients who met the sepsis-3 criteria, of sign of infection and a sequential organ failure assessment (SOFA) score of >= 2. This included patients who had sepsis but not necessarily been recognised by clinicians as doing so. As the data only came from the patient's ICU stay it does mean that the patients identified are perhaps more severely ill than those being treated for sepsis outside the ICU. It also meant it was not possible to differentiate between patients who developed sepsis in the community or in-hospital.

3.3 Data extraction & cleaning

There are many differences between the way CPRD and MIMIC-III are accessed and used. MIMIC-III is free and open access, with potential users required to do an online information governance course and complete a short application form with only a brief overview of the

intended study. They then have access to the complete dataset to download, with separate files for the 26 different tables that make up the relational database. The team behind MIMIC-III provide clear and detailed instructions of how to build the database and how to query it using SQL to extract the required data. Once the database was built, the patients with sepsis were identified then all the necessary data for those unique patient and admission IDs were extracted from the linked tables.

To use CPRD data the process is quite different, they only allow researchers to gain access to the specific data required for their study. The first step was to write and submit an ISAC protocol, detailing the rationale behind the study, the study design, specific covariates that were needed, patient selection criteria and all statistical analyses. This had to be reviewed then approved by the CPRD committee prior to the data being extracted. The data extraction was in two stages, initially CPRD sent through diagnostic details of any hospital admissions with an ICD code for sepsis, as well as hospital admissions with a diagnostic code for a non-infectious condition for the control patients. Exclusion criteria were applied to the potential cohort of patients, then they were split into two subgroups, depending on where they developed sepsis. Control patients for the community-acquired sepsis group were identified in the GP record data and hospital-acquired sepsis controls were identified in the hospital admissions data. The final list of patient IDs were then sent back to CPRD who extracted the full HES record data.

There were some issues around the number of patients and the volume of HES data to be extracted from CPRD, which lead me to restrict the age of the patients in my study to only those who were over 65 at the time of sepsis. Initially, we were planning on carrying out screening of sepsis cases using limited HES diagnostic data then requesting full HES records for all cases and potential eligible controls, then carrying out the case-control matching. Due to the size of this cohort CPRD were unable to carry out the extract so it was necessary to reduce the number of patients and carry out the case-control matching prior to requesting the full HES records. The University of Manchester has a license with CPRD whereby researchers can directly access the primary care record data for patients, from which my supervisor had already extracted data for a cohort of patients over the age of 65 only, for another study. As my project had already experienced significant delays due to COVID-19 and gaining access to data, it was decided to use this reduced dataset to identify eligible control patients for the sepsis cases then only request full HES records for the final cases and controls. Whilst this is a limitation of the studies, it did mean I could begin some preliminary analyses whilst waiting for the HES data extracts and therefore complete analysis within the timeframe of my PhD programme.

Both CPRD and MIMIC-III consisted of data captured in multiple tables, that were linked by unique patient ID's and unique admission or hospital spell ID's. Initial stages of the data cleaning process were largely focussed on extracting data from each table for the patients in my cohort.

In MIMIC-III most of the tables used codes for observations or fluids given, with separate look-up tables defining these codes, diagnostic and comorbidity information was recorded using ICD-9 codes. The details of all the information contained in MIMIC can be found here https://mimic-mit-edu.manchester.idm.oclc.org/docs/iii/tables/. Once the cohort of sepsis patients had been identified the unique patient ID, hospital admission ID and ICU stay ID for the sepsis episode were used to extract antibiotic prescribing data for the admission. The details of the patient's stay including the start and end dates of admissions, patient's date of birth and sex and diagnostic information were extracted from the *admissions, patients, ICU stays* and *diagnoses_icd* tables. Details of how the Elixhauser comorbidity score, SOFA score and Sepsis-3 criteria were calculated are described in the link above and in the MIMIC code repository. https://github.com/MIT-LCP/mimic-code/tree/main/mimic-iii

There were two tables containing antibiotic prescribing data. The *input events* table contained all IV administrations of fluids and drugs solely from the ICU stay which were date and time-stamped. The drugs were not named but given an item ID which could be looked up in a separate table to find the drug name and drug type. Additionally, the *prescriptions* table contained data for all drug prescriptions ordered from throughout the patient's hospital stay (not just in ICU). The prescriptions had a start and end date, dose, and delivery method, but did not detail how many doses per day. For the data in the *prescriptions* table, rather than being labelled with the item IDs used in the *input events* they were labelled with only a text field for the drug name.

The unique patient and hospital admission ID's were used to extract all prescriptions and IV drugs administered from the respective tables for the sepsis admission. To identify the antimicrobials amongst those, I used the drug type variable in the look-up *input events* table to create a list of all the antimicrobial drug codes. For the *prescriptions* table I used the list of antimicrobials from the *input events* table to cross-reference with all the possible drugs prescribed in the *prescriptions* table. There were big inconsistencies with the naming of antibiotics in this field, with multiple different spellings or formatting of the same antibiotics, and whilst most were recorded as their generic name some were recorded under a brand name. This required cleaning, identifying all the possible variations for each antibiotic and recoding the variable with names that matched the names used in the IV drugs table.

As well as cleaning the drug names the following steps were also carried out: removing duplicated entries for the same drug and date/time stamp, removing entries where the recorded date/time stamp did not fall within the recorded admission start and end date, removing prescriptions where there was no start or end date/time stamp recorded, removing entries where the prescription start date or administration date was after the patient's recorded date of death and removing entries where either the drug name or code, the dose or route of administration was missing. Where patients had a prescription starting in the hospital admission before their admission to ICU I assumed that this prescription remained valid on ICU admission. Where patients had consecutive prescriptions for the same drug and dose these were combined into one course. For prescriptions of drugs given through an IV route the corresponding administrations of those in the *input events* table were identified. The antimicrobial exposure for each patient was summarised, the details of this are in section 3.5.8.

In CPRD and HES there were multiple coding systems used to identify diagnoses and comorbidities. HES admissions use ICD-10 codes, CPRD Gold use READ codes and CPRD Aurum use a combination of READ, SNOMED and EMIS web codes. For each of these coding systems there are multiple codes associated with each comorbidity or diagnosis of interest, so it's necessary to compile lists of all codes relevant to a condition. For these studies I mainly used code lists that had been used by my supervisor (TvS) for previous work. There were some comorbidities I was interested for which my supervisor did not have lists for (hypertension, skin ulcers, deep vein thrombosis). To compile these lists I looked them up here: https://clinicalcodes.rss.mhs.man.ac.uk/medcodes/articles/. This repository includes lists used by other researchers in peer-reviewed studies. https://www.phpc.cam.ac.uk/pcu/research/research-groups/crmh/cprd_cam/codelists/v11/

For the comorbid variables in CPRD they were extracted from any point in the patient's observation period up until the index date. For BMI and smoking the most recent measurement to the index date was used and if patients did not have a BMI recorded but had a height and weight measurement then BMI was calculated from these. The antibiotic prescription data was extracted using code-lists created from the BNF for the period between the index date and a maximum of 3 years prior to this. Exact duplicates were removed as well as prescriptions with no drug name recorded or dose. Where there were multiple entries on the same date for the same drug but a different dose these were combined into one course.

As with all electronic health record data there are issues and inaccuracies within the datasets that need to be identified. Missing data is a common issue. In CPRD there are some variables that are not consistently recorded, including BMI and smoking status. There are also

differences between the two datasets in CPRD, which could be down to the different EHR systems used or behavioural differences in the clinicians. For example, in my cohort smoking status was recorded for more patients in the Gold dataset, with a lower proportion of "current smokers", whereas patients in the Aurum dataset were less likely to have a record of smoking status but of those who did there was a greater proportion who smoked. For patients with a missing BMI measurement it may be possible to calculate that if they have a measurement for both height and weight recorded. There are different ways to deal with missing data, depending on the patterns of missing-ness and the type of analysis being done. There is an underlying bias in any source of EHR data, in that patients who are less healthy will have contact with healthcare more frequently, and therefore will contribute more data[7,8].

3.4 Study design

For the study using MIMIC-III data (Chapter 5) I used a retrospective cohort study. Patients entered the study when they were admitted to the ICU with sepsis and were followed up for a maximum of 30 days. I did not include any control patients in this study.

In the two studies using CPRD data I also used a retrospective cohort study. For the first study (Chapter 4) where I was looking at risk factors associated with developing sepsis I identified patient's index dates as the date they were either admitted to hospital with sepsis or their sepsis episode began in hospital. I looked back at a 1 to 3 year period before their index date. All patients within the study had a minimum of 1 year prior follow-up, and a sub-cohort of patients had a maximum of 3 years.

For the second CPRD study (Chapter 6) I used the same cohort of patients, removing those who had not survived their sepsis admission. The patients were given a new index date of the date they were discharged from hospital then followed up for a maximum of 3 years.

I identified control patients for all sepsis cases using a matched case-control approach. This involved identifying patients from an eligible pool who matched the case patients on specific criteria. I matched community-acquired sepsis cases to patients on age (within a range of 5 years), sex, GP, and calendar time. Matching on GP and calendar time reduces variation between how patient information is recorded at each practice and how the way information is recorded can change over a time period. For the controls for hospital-acquired sepsis patients I did not match on GP practice instead on duration of hospital stay, to ensure that the control patients had been in hospital for at least as long as the sepsis patients were before they developed sepsis. Unfortunately, it was not possible to match the patients by hospital. There were some problems with matching on duration of stay, it was difficult to find the maximum

number of controls for every case. So rather than reduce the sample size I included controls with a shorter hospital length of stay and conducted some sensitivity analyses excluding them. For both sets of cases I aimed to find 6 controls per sepsis patient. For more common conditions it is acceptable to match patients on a 1:1 basis, however as sepsis is a relatively rare condition it is recommended to go for a higher number of controls, to ensure enough statistical power.

The alternative to this approach would have been propensity score matching, where a model is used to calculate a score based on the covariates of interest then cases are matched to controls with the closest score. There are advantages and disadvantages to both methods.

3.5 Defining exposures, outcome variables & comorbidities

Once data has been extracted from EHR records and undergone initial cleaning, there are further steps that need to be undertaken to create specific variables needed. Additionally, I will give details here of some of the pre-existing scores used e.g. IMD.

3.5.1 Body Mass Index (BMI)

BMI is calculated by dividing a person's weight in kilograms by their height in metres, squared. The measurement can be grouped as follows: BMI less than 18.5 kg/m^2 – underweight, BMI between 18.5 and 24.9 kg/m^2 – normal range, BMI between 25 and 29.9 kg/m^2 – overweight, BMI more than 30 kg/m^2 – obese. Where patients had multiple entries for BMI the one closest to index date was used.

3.5.2 Comorbidities

As mentioned in section 3.3 there are different code systems used by the EHR systems, once the code lists had been compiled they were used to extract information for each included patient in the studies. The lists of codes used in these studies can be found in the supplementary materials/ appendices.

For the studies using CPRD there was an additional factor to consider, in that not every comorbidity will be recorded by a GP at every consultation, so all though I was interested in antibiotic prescribing in the 3 year period prior to sepsis we used the full period between the start of patient's data collection in CPRD to their index date for detection of comorbidities.

The way these comorbidity variables were coded for each patient was as a binary variable, 1 if any of the codes for the condition were present in the patient's record, and a 0 if not. Depending on the study, additional scores to indicate overall comorbidity levels for each patient were calculated, the Elixhauser comorbidity index for the MIMIC-III study and the Charlson comorbidity index for the two studies using CPRD data.

3.5.3 Charlson comorbidity index

The Charlson comorbidity score[9] was initially developed as a score to predict 10-year mortality risk and is calculated by scoring the presence of a defined list of comorbidities, weighting them then adding them up to give a total score. The overall score was then grouped as follows; 0, 1-2, 3-4, 5-6, 7+. The comorbidities and weightings that make up the score are as follows[9]:

1. 1 point - myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, dementia, connective tissue disease, peptic ulcer disease, mild liver disease & diabetes
2. 2 points – hemiplegia, moderate or severe renal disease, diabetes with end-organ damage, localised solid tumour, leukaemia & lymphoma
3. 3 points – moderate or severe liver disease
4. 6 points – metastatic solid tumour & AIDS

3.5.4 Elixhauser index

The Elixhauser index[10] is a similar comorbidity score based on ICD codes. It includes a more comprehensive list of conditions than the Charlson score but was developed in a similar way, identifying factors associated with mortality and weighting them according to severity. The higher the overall comorbidity score the worse the outcomes are. The system was initially a set of 30 separate comorbidities[11] but in 2008 an index was developed[10], summarising overall comorbidity levels. The index was developed using a multivariable logistic regression model, with in-hospital mortality as the outcome. All 30 comorbidities were included as potential predictors then backward selection used to select the final variables and the coefficient estimates converted into the index below. For the comorbidities with a negative score these were associated with a decreased risk of in-hospital death in the adjusted model. The researchers hypothesised that this may be due to a bias in the way some comorbidities were coded in less severely ill patients. Comorbidities that are less immediately threatening to life, for example obesity or depression, may be more likely to be coded in less severely ill patients

with fewer other serious comorbidities. The index was validated in a large cohort and had higher discrimination than the Charlson comorbidity score. A strength of the Elixhauser index is that in the derivation study the comorbidity diagnoses were all available at the point of admission to hospital, not prior or in-hospital information. A few studies have shown that the Elixhauser index performed better than the Charlson comorbidity index at predicting in-hospital mortality[12,13]. As we were interested in predicting short-term mortality and the fact that the index score was pre-calculated for patients in the MIMIC-III database is why it was chosen for the analysis in Chapter 5. The comorbidities used in Elixhauser are as follows[10]:

1. -7 points – drug abuse
2. -4 points – obesity
3. -3 points – depression
4. -2 points – deficiency anaemia & blood loss anaemia
5. -1 points – valvular disease
6. 0 points - hypertension, uncomplicated and complicated diabetes, hypothyroidism, peptic ulcer disease, AIDS/HIV, rheumatoid arthritis, alcohol abuse & psychosis
7. 2 points – peripheral vascular disorders
8. 3 points – chronic pulmonary disease & coagulopathy
9. 4 points – pulmonary circulation disorders & solid tumour without metastatis
10. 5 points – cardiac arrhythmias, renal failure & fluid and electrolyte disorders
11. 6 points – neurodegenerative disorders & weight loss
12. 7 points – congestive heart failure & paralysis
13. 9 points – lymphoma
14. 11 points – liver disease
15. 12 points – metastatic cancer

3.5.5 Sequential Organ Failure Assessment (SOFA) score

The Sequential (originally sepsis-related) Organ Failure Assessment (SOFA) score was developed by Vincent et al in 1996[14] and was designed to empirically quantify and track levels of organ dysfunction over a period of severe illness and is widely reported in sepsis research in ICU. There are six organ systems assessed, which are the respiratory system, coagulation, the liver, the cardiovascular system, the central nervous system, and the renal system. Each system is scored from 0 to 4, where 0 is normal function and 4 is the highest level of dysfunction, according to the criteria in Table 4.1 below. For the MIMIC-III study the SOFA score was calculated using the lowest/highest measurements during the first 24 hours of a patient's ICU stay.

Organ System	Measurement	Range per score			
		1	2	3	4
Respiratory	PaO_2/FiO_2, mmHg	<400	<300	<200	<100
Coagulation	Platelets x $10^3/mm^3$	<150	<100	<50	<20
Liver	Bilirubin, mg/dl	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular	Blood pressure	Mean arterial pressure <70 mmHg	Dopamine ≤5	Dopamine >5, Epinephrine ≤0.1, norepinephrine ≤0.1	Dopamine >15, Epinephrine >0.1, norepinephrine >0.1
Central Nervous System	Glasgow Coma Score	13-14	10-12	6-9	<6
Renal	Creatine, mg/dl or urine output	1.2-1.9	2.0-3.4	3.5-4.9, <500ml/day	>5.0, <200ml/day

Table 3.1 *Sequential Organ Dysfunction Assessment (SOFA) score.* Adapted from Vincent et al[14] (page 2)

3.5.6 Smoking status

In CPRD smoking status is recorded as either non-smoker, ex-smoker or current smoker.

3.5.7 Index of Multiple Deprivation (IMD)

For the CPRD studies I have used the index of multiple deprivation (IMD) index, which is a UK socioeconomic score composed of 37 different indicators across domains covering employment, healthcare, crime, education and others. The deprivation index is calculated per Lower-layer Super Output Area then areas are ranked from least deprived to most deprived[15]. The index was provided by CPRD in quintiles where patients with a score of 1 were in the least deprived areas, and patients with a score of 5 were in the most deprived areas.

3.5.8 Antibiotic exposure

Depending on the study there were different methods to summarise antibiotic use in patients. For the MIMIC-III study the number of courses of antibiotics for each patient was calculated, along with the total number of exposure days where days were counted only once, even if they were given more than one antibiotic on the same day. Additionally the number of cumulative exposure days where days were counted multiple times if the patient had received more than one type of antibiotic on the same day. For example, in the figure below the patient

has received 2 different courses of antibiotics over a total of 5 days, however the drugs have overlapped by 1 day, so the cumulative number of exposure days would be 6.

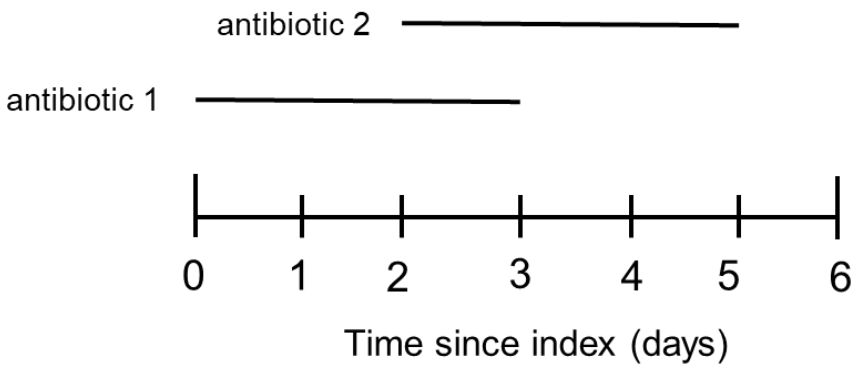


Figure 4.1 *Example of a patient's antibiotic use.*

For the CPRD studies the number of antibiotics per patient was calculated for either the 3-year or 1-year period either side of the sepsis episode. Where patients had multiple antibiotics prescribed on the same day only 1 was counted. For the study looking at risk factors associated with sepsis the number of prescriptions was grouped as follows: 0, 1, 2, 3-4, 5-6 and 7+ for 1-year, and 0, 1, 2, 3-4, 5-7, 8-12 and 13+ for the patients with 3-years of prior follow-up. For the other measure of antibiotic use comparing usage prior and post-sepsis it was necessary to calculate use as a rate per 1,000 patients per week. This was to take into account the fact that during the post-sepsis follow-up period patients were lost-to-follow up through either dying or leaving their GP practice.

3.5.9 Outcomes

For the MIMIC-III study the primary outcome was 30-day mortality, this was recorded in the patients table in the database, and flagged as either an in-hospital death or a death outside of hospital confirmed by social security data.

The primary outcome in the first CPRD paper is whether or not patients had developed sepsis, recorded using a binary variable. Controls were recorded as 0 and sepsis cases with a 1. An additional variable flagged patients as either community-acquired (1) or hospital-acquired (0) patients.

For the final CPRD paper the primary outcome was mortality at either a 1-year or 3-year time point. The dates of death were taken from the ONS data. Additional outcomes were hospital readmissions which were identified in the HES records and rates of common infection, which

were identified in CPRD records. Similar to comparing antibiotic use the rates of common infections were calculated as a rate per 1,000 patients per week, to take into account patients lost to follow-up.

3.6 Analyses

3.6.1 Missing data

There are different ways to deal with missing data depending on the mechanism of missingness. There are three categories of missingness: missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR). MCAR is when data are missing completely at random and the patients who do not have data recorded are representative of those that do. MAR is when missingness of a variable is associated with other measured variables in the dataset, for example an older patient may be more likely to have a measurement taken than a younger patient. MNAR occurs when missingness is associated with the value of the measurement itself or other variables that have not been measured in the dataset[16,17]. Complete case analysis, where only patients with no missingness values are used in analysis, can reduce the sample size and introduce bias when the missingness is not MCAR. The missing indicator method is where a variable is created to indicate whether an individual has a measurement recorded or not, then this is included in the analysis. Whilst this does have advantages over complete case analysis in that the sample size is not reduced it has been shown to introduce bias[18,19]. Another approach is imputation, where the missing value is imputed from a regression model including the other variables and predictor. This is either done once (single imputation) or numerous times (multiple imputation) and analysis carried out separately in each. Multiple imputation is a more robust method of handling missing data when data is MCAR, however, when data is MNAR multiple imputation has been shown to be biased[20]. It can also be computationally intensive when used with large datasets.

In the CPRD & HES data the covariates of interest with missing data were smoking status, BMI and IMD. The percentage of patients with missing data was 40.4% for smoking status, 52.5% for BMI and 1.2% for IMD in the initial full cohort. A missing indicator method was used in these studies. This was partly due to the size of the cohort and proportion of missing data and the implications of this in terms of computation and time. Additionally, it was not clear what the missingness mechanism for the three variables was. The proportion of patients in the Gold and Aurum cohorts with missing values for smoking status differed, with 7.2% of Gold and 46.2% of Aurum patients with missing data. Of those with their smoking status recorded there

were 12.0% of Gold patients and 30.0% of Aurum patients categorised as current smokers. Similarly there was a much higher proportion of patients in Aurum with a missing BMI measurement than Gold. There were no clear reasons for these differences. Patients who do smoke may be more likely to be recorded as doing so if asked by a clinician, but it is not clear why there are differences between the two databases. As I could not be certain the data was MAR it did not seem appropriate to use multiple imputation.

For smoking status and IMD an additional level was created and all patients with missing values were assigned to that level. For BMI the continuous measurement was grouped as a categorical variable and a separate level created for those with a missing measurement.

3.6.2 Variable selection

For the conditional logistic regression model in study 1, the Cox proportional hazards regression and Fine-Gray competing risks models in study 3, the comorbidity variables selected for inclusion into the models were identified from previously published studies as risk factors for sepsis or poor outcomes. Neither sex nor age were included in the conditional logistic regression model as they had been used as variables to match the case and controls. There was no statistical method (e.g. forward/backward selection) used to select the final variables to include in the models, as the cohort size was large the risk of overfitting was minimal. The Charlson comorbidity score was also calculated in both studies and included in univariate models, as I was interested in assessing the association between overall comorbidity levels and risk of sepsis or poor outcomes. This score was not included in the fully adjusted model, however, as there would be issues with correlation with the individual comorbidity variables.

For the survival analysis conducted in study 2 using the MIMIC-III data it was decided to include the Elixhauser score as an overall measure of comorbidity rather than individual ones. This was due to the smaller cohort size in this study and the low prevalence of some of the comorbidities of interest in the sample.

3.6.3 Conditional logistic regression

Logistic regression models are a type of generalised linear model where the outcome is binary, for example whether or not a patient develops sepsis. Like in linear regression the relationship between the outcome and a linear predictor of predictors and regression coefficients is modelled. Rather than modelling the value of the response variable however, logistic

regression gives the probability of the response occurring, between 0 and 1, through the use of a logistic link function (or logit). The equation for a logistic regression model is as follows[21]:

$$logit\big(P(Y=1)\big) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k$$

Where Y is the response variable (i.e. development of sepsis), β_0 is the intercept, $X_1 - X_k$ are the covariates of interest and $\beta_1 - \beta_k$ are the regression coefficients estimated through the maximum likelihood. The exponential of the β's is the odds ratio (OR). An OR of 1 means that the predictor has no effect on the outcome (given that other predictors are constant). An OR of less than 1 means that the predictor decreases the probability of the outcome occurring and an OR of more than 1 means the predictor increases the risk[21].

The matched case-control design of our study meant it was necessary to use a conditional logistic regression model, to adjust for the potential confounders. When performing conditional logistic regression a strata variable is included, indicating the sets of matched cases and controls, with the comparison between cases and controls only happening within each strata[21,22].

For each logistic regression model used I ran them separately with each individual covariate to calculate an unadjusted odds ratio, then a fully adjusted model with all covariates together.

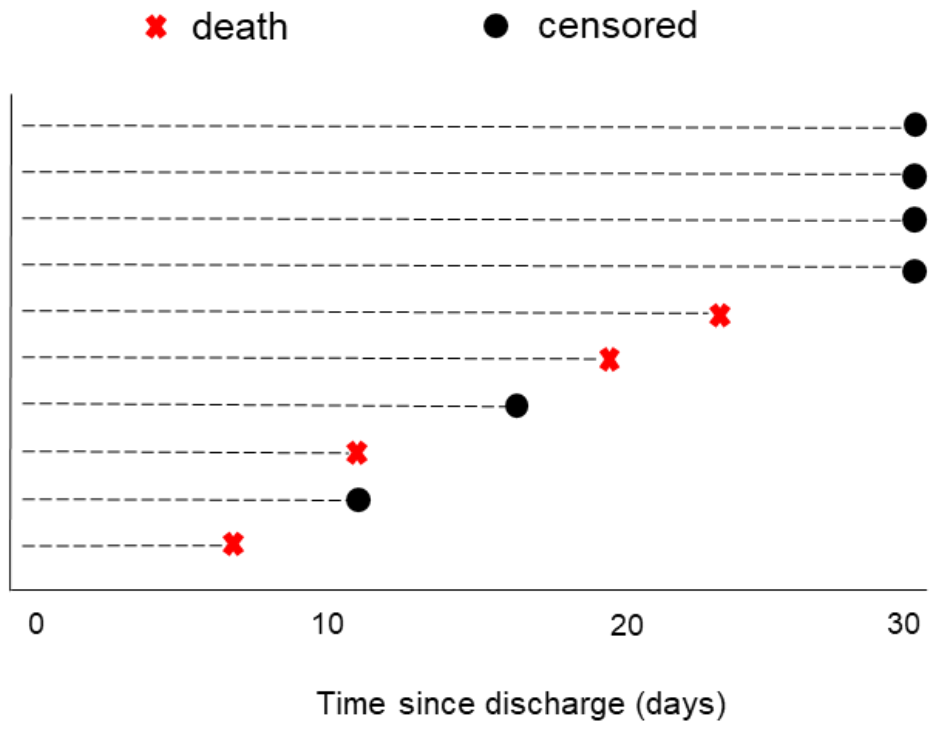
3.6.4 Survival analysis – Kaplan-Meier

Survival (or time-to-event) analysis is used to model the probability of an event occurring within a certain time period. The most common use is to model time until death (hence survival) however it can also be used for other outcomes such as readmission to hospital after discharge, or time to recovery after a procedure or treatment. Survival analysis has to take into account that patients may have different lengths of follow-up time, which it does by censoring. For example, you may be interested in the time until death following a surgical procedure and wanted to follow-up patients for a maximum of 1 year. Some patients would experience the event within that year, but others may be lost to follow-up for various reasons, and are therefore censored. Patients who reach the end of the study period without dying are also censored at that point[21].

Kaplan-Meier analysis can be used to estimate the survivor function, or S(t), which is the probability that a person survives (or does not experience the event of interest) longer than a

certain time, t. At each time point the number of surviving patients is divided by the number of patients still at risk, then multiplied by the probability of surviving up until that time point[23]. See the figure below for an example, where each dashed line represents one of ten individual patient who are being followed up for a maximum of 30 days following hospital discharge. Deaths during the follow-up are represented by a red cross, and censored patients by a black circle. The table underneath displays the number of patients at risk, number of events and censored and the cumulative survival probability at each time point.

Kaplan-Meier plots are often used to visualise the cumulative survival over time, and can be used to compare different groups of patients by stratifying. Log-rank tests can be used to test whether the survival of different groups is statistically significant[24].



Time (days)	7	12	17	20	24	30
No. at risk	10	9	7	6	5	4
No. events	1	1	0	1	1	0
No. censored	0	1	1	0	0	4
Cumulative survival	9/10 = 0.9	8/9 x 0.9 = 0.8	7/7 x 0.8 = 0.8	5/6 x 0.8 = 0.67	4/5 x 0.67 = 0.53	4/4 x 0.53 = 0.53

Figure 3.2. *Example of estimating survival probability using Kaplan-Meier analysis.* Adapted from Harrell et al[21] (figure page 407 and table page 410)

3.6.5 Survival analysis – Cox proportional hazards regression

An alternative method of survival analysis is the Cox proportional hazards model, which uses a hazard function to estimate the rate of the event occurring after a certain time, t, given that the patient is still alive at time t. Similarly to generalised linear regression models, including covariates in the model can assess the effect of these predictors on survival time. The formula for the Cox model is as follows[21]:

$$h(\mathrm{t}) = h_0(t) \exp\left(\beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k\right)$$

Where h_0(t) is the baseline hazard, $X_1 – X_k$ are the covariates of interest and $\beta_1 – \beta_k$ are the coefficients. It is not always necessary to estimate the baseline hazard, but by taking the exponential of the β's you get the ratio of the hazard function at time t, otherwise known as the hazard ratio (HR). A HR of 1 means that a change in the value of the predictor does not have an effect on the hazard function (if other X's remain constant), a HR of more than 1 would mean there is an increase in the hazard function and a HR of less than 1 would mean a decrease in hazard function[21].

There are assumptions to be aware of with the proportional hazards model, the main one being that the baseline hazard remains constant for all patients. If this assumption is violated then there a number of ways to deal with that, including stratifying by the variable that is violating the assumption. For continuous variables you can transform the variable or use a more complex approach such as restrictive cubic splines or fractional polynomials[25].

In the MIMIC-III study patients were followed up from admission to ICU for a maximum of 30 days, but the exposure of interest, antibiotic use, changes over the 30 days. This means it needs to be included in the model as a time-varying covariate. Usually when preparing data for Cox regression modelling each patient will have a single row of data, containing either the date of death or censoring, an event flag, and the other variables of interest. For Cox analysis with a time-varying covariate patients will have multiple rows of data, with the overall time period split up into different periods determined by changes in the antibiotic exposure which in this study was the start of a new prescription. At each time point the model then compares the risk of death between patients of different exposure levels at that specific time point, as well as incorporating the values of the other variables at baseline[26].

3.6.6 Survival analysis – Competing risks

For scenarios where there is a competing event to your event of interest Kaplan-Meier estimates and Cox proportional hazards regression may not be appropriate, as they can lead to biased estimates in the risk of events occurring[27]. For example, you might be interested in deaths from a specific cause, but death from any other cause is a competing event. In the context of this thesis, in Chapter 6 the event of interest is hospital readmission following survival of a sepsis episode, with death as the competing event.

The cumulative incidence function (CIF) can be used to model the incidence of an outcome in the presence of competing risks. Similar to the Kaplan-Meier estimates this can be visualised using cumulative incidence plots and stratified by covariates of interest.

The two most common ways to model the effects of covariates on the CIF are the cause-specific hazard and the subdistribution hazard functions. Modelling the cause-specific hazard function involves censoring patients if they have experienced the competing event and estimating the rate of the main event in only patients who have not experienced either event [28]. However, this approach assumes that the censoring is non-informative and can lead to biased estimates when the competing events are not independent.

The other approach is to model the subdistribution hazard function, which estimates the rate of the main event occurring in those who have not yet experienced that event, but can have experienced the competing event[29]. Patients who experience the competing event are not censored but are left in the "at risk" group for the main event of interest. This method is commonly known as the Fine-Gray model[30].

For the analyses in Chapter 6 a Fine-Gray model was chosen to be the most appropriate as readmission to hospital and death following sepsis are unlikely to be independent of one another. Some of the covariates considered (e.g. Charlson comorbidity score) are likely to be risk factors for both outcomes and therefore the non-informative censoring assumption would not hold.

3.7 References

1. Herrett, E. *et al.* Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* **44**, 827–836 (2015).

2. Wolf, A. *et al.* Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. *Int J Epidemiol* **48**, 1740-1740G (2019).

3. Herbert, A., Wijlaars, L., Zylbersztejn, A., Cromwell, D. & Hardelid, P. Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). *Int J Epidemiol* **46**, 1093 (2017).

4. Padmanabhan, S. *et al.* Approach to record linkage of primary care data from Clinical Practice Research Datalink to other health-related patient data: overview and implications. *Eur J Epidemiol* **34**, 91–99 (2019).

5. Rezel-Potts, E. *et al.* Sepsis recording in primary care electronic health records, linked hospital episodes and mortality records: Population-based cohort study in England. *PLoS One* **15**, (2020).

6. Johnson, A. *et al.* MIMIC-III, a freely accessible critical care database. *Sci Data* **3**, 1–9 (2016).

7. Rusanov, A., Weiskopf, N. G., Wang, S. & Weng, C. Hidden in plain sight: Bias towards sick patients when sampling patients with sufficient electronic health record data for research. *BMC Med Inform Decis Mak* **14**, 1–9 (2014).

8. Goldstein, B. A., Bhavsar, N. A., Phelan, M. & Pencina, M. J. Controlling for Informed Presence Bias Due to the Number of Health Encounters in an Electronic Health Record. *Am J Epidemiol* **184**, 847–855 (2016).

9. Charlson, M. E., Pompei, P., Ales, K. L. & MacKenzie, C. R. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* **40**, 373–383 (1987).

10. Van Walraven, C., Austin, P. C., Jennings, A., Quan, H. & Forster, A. J. A modification of the elixhauser comorbidity measures into a point system for hospital death using administrative data. *Med Care* **47**, 626–633 (2009).

11. Elixhauser, A., Steiner, C., Harris, D. R. & Coffey, R. M. Comorbidity Measures for Use with Administrative Data. *Med Care* **36**, (1998).

12. Sharma, N., Schwendimann, R., Endrich, O., Ausserhofer, D. & Simon, M. Comparing Charlson and Elixhauser comorbidity indices with different weightings to predict in-hospital mortality: an analysis of national inpatient data. *BMC Health Serv Res* **21**, (2021).

13. Cai, M. *et al.* Comparing the performance of charlson and elixhauser comorbidity indices to predict in-hospital mortality among a Chinese population. *Clin Epidemiol* **12**, 307–316 (2020).

14. Vincent, J.-Louis. *et al.* The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med* **22**, 707–710 (1996).

15. UK Government. *The English Indices of Deprivation 2015*. *Department for Communities and Local Government* (2015).

16. Lee, K. J., Carlin, J. B., Simpson, J. A. & Moreno-Betancur, M. Assumptions and analysis planning in studies with missing data in multiple variables: moving beyond the MCAR/MAR/MNAR classification. *Int J Epidemiol* (2023) doi:10.1093/ije/dyad008.

17. Steyerberg, E. *Clinical Prediction Models - A practical approach to development, validation, and updating*. *Journal of Chemical Information and Modeling* vol. 53 (Springer New York, 2009).

18. Knol, M. J. *et al.* Unpredictable bias when using the missing indicator method or complete case analysis for missing confounder values: an empirical example. *J Clin Epidemiol* **63**, 728–736 (2010).

19. Groenwold, R. H. H. *et al.* Missing covariate data in clinical research: When and when not to use the missing-indicator method for analysis. *CMAJ* **184**, 1265–1269 (2012).

20. White, I. R. & Carlin, J. B. Bias and efficiency of multiple imputation compared with complete-case analysis for missing covariate values. *Stat Med* **29**, 2920–2931 (2010).

21. Harrell Jr., F. E. *Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis*. *Springer Series in Statistics* (Springer International Publishing, 2015). doi:10.1177/096228020401300512.

22. Hosmer, D. W., Lemeshow, S. & Sturdivant, R. X. *Applied Logistic Regression*. *Biometrics* vol. 47 (Wiley, 2013).

23. In, J. & Lee, D. K. Survival analysis: Part I - Analysis of time-to-event. *Korean Journal of Anesthesiology* vol. 71 182–191 Preprint at https://doi.org/10.4097/kja.d.18.00067 (2018).

24. Morris, T. P. *et al.* Proposals on Kaplan–Meier plots in medical research and a survey of stakeholder views: KMunicate. *BMJ Open* **9**, e030215 (2019).

25. Sauerbrei, W. *et al.* State of the art in selection of variables and functional forms in multivariable analysis—outstanding issues. *Diagn Progn Res* **4**, (2020).

26. Zhang, Z., Reinikainen, J., Adeleke, K. A., Pieterse, M. E. & Groothuis-Oudshoorn, C. G. M. Time-varying covariates and coefficients in Cox regression models. *Ann Transl Med* **6**, 121 (2018).

27. Austin, P. C., Putter, H., Lee, D. S. & Steyerberg, E. W. Estimation of the Absolute Risk of Cardiovascular Disease and Other Events: Issues With the Use of Multiple Fine-Gray Subdistribution Hazard Models. *Circ Cardiovasc Qual Outcomes* **15**, e008368 (2022).

28. Putter, H., Schumacher, M. & van Houwelingen, H. C. On the relation between the cause-specific hazard and the subdistribution rate for competing risks data: The Fine–Gray model revisited. *Biometrical Journal* **62**, 790–807 (2020).

29. Austin, P. C. & Fine, J. P. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. *Stat Med* **36**, 4391–4400 (2017).

30. Fine, J. P. & Gray, R. J. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *Source: Journal of the American Statistical Association* **94**, 496–509 (1999).

Chapter 4 - Risk factors for development of sepsis – a retrospective study using linked English primary and secondary care data

4.1 Abstract

Background: Sepsis ("life-threatening organ dysfunction caused by a dysregulated host response to an infection") is a serious condition associated with around 50,000 deaths in the UK each year. There are a number of risk factors associated with sepsis including age and comorbidity levels. Antibiotics are crucial to manage sepsis, however, with emerging resistance there is a need to reduce and optimise antibiotic use.

Aims: to use linked primary and secondary care data to investigate risk factors for developing sepsis including demographic, comorbid and antibiotic use factors and to determine whether these differ in patients with community or hospital-acquired sepsis.

Methods: Patients with an ICD-10 diagnosis of sepsis in hospital admissions (HES) records were identified and divided into community-acquired and hospital-acquired sepsis (sepsis episode started more than 2 days after admission). Hospital-acquired sepsis cases were matched to controls in HES records with a non-infection hospital admission, community-acquired cases were matched to population based controls from primary care (CPRD) records. For all patients CPRD data was extracted for a minimum of 1 year prior to index. Conditional logistic regression was used to identify variables (demographics, comorbidities and antibiotic exposure) associated with risk of developing sepsis separately for community-acquired and hospital-acquired patients.

Results: There were 120,580 sepsis patients, of which 92.1% were community-acquired sepsis patients. A total of 705,959 eligible controls were identified. Community-acquired sepsis patients had higher comorbidity scores and prior antibiotic use than their respective controls, however for the hospital-acquired group the levels were similar between cases and controls. For patients in the community-acquired group deprivation score (most deprived quintile OR 1.30, 95% CI 1.26-1.34), Charlson comorbidity score (score 7+ OR 5.57, 95% CI 5.40-5.75) and antibiotic use (no. of prescriptions 7+ OR 2.98, 95% CI 2.89-3.07) was associated with increased risk of developing sepsis. In the hospital-acquired group similar association was there for deprivation (most deprived quintile OR 1.28, 95% CI 1.20-1.36) but not for Charlson score (score 7+ OR 1.06, 95% CI 0.97-1.17) or prior antibiotic use (OR 1.19, 95% CI 1.09-1.29). Hospital-acquired sepsis patients had higher in-hospital mortality (46.3%

vs 37.9%) and hospital length of stay (21 vs 11 days) than community-acquired sepsis patients.

Conclusion: There are differences in risk factors for community-acquired and hospital-acquired sepsis. Prior antibiotic prescribing was associated with an increased risk of community-acquired sepsis, potentially through altering the gut microbiome. Unnecessary antibiotic prescribing should be avoided to reduce the risks of complications such as sepsis.

4.2 Introduction

Sepsis is defined as "life-threatening organ dysfunction caused by a dysregulated host response to an infection"[1]. An estimated 250,000 people develop sepsis each year in the UK, causing approximately 50,000 deaths[2]. Additionally, many patients who survive an episode of sepsis suffer from long-term conditions and require an increased level of care[3–5].

Due to the severity of sepsis it is frequently diagnosed and treated in secondary care. However, the majority of sepsis patients will develop it in the community. Two US studies reported that between 79-85% of sepsis cases developed in the community, with the remainder contracting sepsis during a hospital admission[6,7]. There are studies using electronic health record (EHR) data to predict development of sepsis and outcomes, however, they mostly use secondary care data on admission to hospital[8–10]. There are no studies we are aware of using linked primary and secondary care data to look at risk factors for sepsis prior to hospital admission.

There are a number of established risk factors associated with developing sepsis, including frailty and co-morbidities such as type 2 diabetes, cancer, cardiovascular disease, lung disease and chronic kidney disease[11]. Age is strongly associated with an increased risk of sepsis, with the majority of cases occurring in patients over the age of 65[12,13]. Much of the research, however, does not differentiate between patients with community-acquired or hospital-acquired sepsis though. Patients who develop sepsis in hospital have been shown to have longer lengths-of-stay as well as higher mortality rates[6,14]. This could be due to them being at greater risk of healthcare-acquired infections following a surgical procedure or insertion of a urinary or venous catheter[15].

Prompt treatment with antibiotics is recommended to manage sepsis[1] but, there is also a need to reduce overall consumption of antibiotics to combat the rise in antimicrobial resistance and ensure their continued use in the future[16]. Prolonged or unnecessary antibiotic use in individual patients is thought to be detrimental as it could lead to changes in their microbiota and increase the risk of being infected with a resistant microorganism[17]. However, a recent

study looking at antibiotic prescribing at a practice level found that practices with higher levels of antibiotic prescribing had lower rates of hospital admissions for infection-related complications, including sepsis[18]. A 2020 study using UK primary care data reported that the probability of sepsis was lower if an antibiotic had been prescribed in the previous 30 days, although it only focused on the period immediately prior to sepsis[19]. It is important going forward that initiatives to drive the lowering of antibiotic consumption in primary care do not harm those patients who need them most. Being able to identify patient's at greater risk of developing sepsis in the community could help inform clinician's when deciding whether to prescribe antibiotics.

The overall aim of this study is to use linked primary and secondary EHR data to explore the risk factors associated with developing sepsis, including previous antibiotic use, in order to identify people most at risk. Specifically, objectives were to (i) identify demographic and comorbid factors associated with developing sepsis, (ii) evaluate whether these risk factors differ between patients who develop sepsis in the community or in hospital and (iii) whether history of regular antibiotic use associated with an increased risk of developing sepsis.

4.3 Methods

4.3.1 Data Source

The study used anonymised, routinely collected electronic health record data from the Clinical Practice Research Datalink (CPRD). CPRD collects data from UK general practices (GPs) and consists of two databases of patients, Aurum and Gold. CPRD Aurum contains records from over 44 million current and historic patients from GPs using EMIS software, and covers over 19% of the current UK population[20,21]. CPRD GOLD covers approximately 11 million patients from practices using Vision software, and covers around 4.5% of the UK population[21,22]. Hospital Episode Statistics (HES) records cover admissions to all NHS hospitals in England[23]. Linkage of GP data to HES records was therefore only available for patients in England (linkage set 20, 9.2 million patients in Gold, 35.5 million in Aurum). Additional linkage was also available to Index of Multiple Deprivation (IMD) scores, a measure of deprivation published by the UK government by lower super output area[24]. Areas are ranked in order of least to most deprived and split into quintiles. The study was approved by the CPRD Independent Scientific Advisory Committee (see thesis appendix for protocol).

4.3.2 Patient Selection

Patients with a diagnosis of sepsis between 01/01/2000 and 01/01/2020 were identified from HES records using ICD-10 codes. If a patient had more than one admission for sepsis within the time frame the earliest one was used as the index date. In order to identify incident sepsis only, patients were excluded if they had any historic record of sepsis in their GP records (> 14 days before hospital admission). Patients were also excluded if their sepsis admission was either before the start of, or after the end of their CPRD registration period, or if they had less than one year between start of CPRD registration and the date of their sepsis admission. All patients had at least one year of GP records prior to their index date, with a smaller subgroup having at least three years minimum.

In addition, due to an issue with the size of the data extract requested from CPRD, patients below the age of 65 were excluded to reduce the sample size and therefore the size of the data sets. Primary care record data was already extracted for patients over the age of 65 so to avoid further delays in getting access to the data this was used to begin analyses whilst waiting for HES record data (see Methods section 3.3 for further details).

Patients were categorised as having community-acquired sepsis or hospital-acquired sepsis, depending on when their sepsis episode started within the hospital admission. HES records provided by CPRD gave a start and end date for each hospital admission and the episodes of care that make up each admission, along with diagnostic ICD-10 codes for each period and a unique ID to link different episodes of the same admission. As there were no time stamps available, only dates, a window of two full calendars was used to define community- and hospital-acquired sepsis. Patients were identified as having community-acquired if they had a sepsis ICD code in the episode that started on the date of admission to hospital or up to 2 calendar days after. Patients were identified as having hospital-acquired sepsis if their sepsis episode started more than two calendar days after admission to hospital. Figure 1 shows an example.

All patients were matched on a ratio of 1:6 with controls, and matched on age (stepwise ± 5 years), sex, and calendar time. For community sepsis patient's controls were identified in primary care records and were additionally matched on GP practice. Controls for the hospital-acquired sepsis patients were identified in HES records with a non-infectious diagnosis and were also matched on the number of days in hospital prior to the index date. Potential controls were excluded if they had less than a minimum of one year of GP records before their index date, if they had a record of sepsis in their GP records, and if they had a hospital admission less than two weeks before. For the potential hospital-acquired sepsis controls they were excluded if their hospital admission was outside of the period of GP registration.

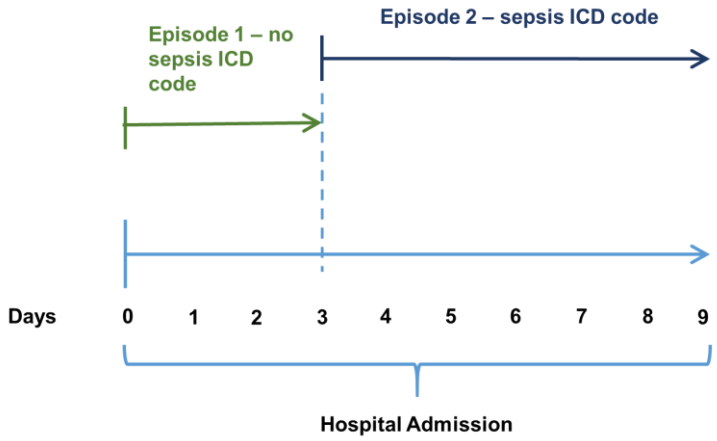


Figure 4.1 *Example timeline for a patient classed as having hospital-acquired sepsis.*

The matching was done in an iterative process. The first iteration matched cases to potential controls on exact age, then the controls were checked for eligibility. The next iteration matched cases to controls on age + 1, then age – 1 and so on until each case had a maximum of six controls. For the community-acquired sepsis controls they were matched first on exact GP practice, then if cases had fewer than six controls the matching process was repeated with patients from other GP practices. For hospital controls where there were not enough controls when matching on duration prior to index, potential controls with a shorter duration were included, a sensitivity analysis excluding controls with a short duration was conducted, see Table S4.9). Following this, any sepsis patients who had no eligible matched controls were excluded from the cohort.

4.3.3 Analyses

The variables of interest included basic demographics (age, sex, ethnicity, body mass index (BMI), smoking status, and index of multiple deprivation (IMD) score), individual comorbidities (cancer, cerebrovascular disease (CVD), chronic obstructive pulmonary disease (COPD), heart failure, dementia, diabetes, HIV, liver disease, moderate/severe renal disease, peripheral vascular disease (PVD), autoimmune disease, coronary heart disease (CHD), skin ulcers, hypertension and deep vein thrombosis (DVT)), primary care consultations for common infections (upper respiratory tract infection (URTI), lower respiratory tract infection (LRTI), urinary tract infection (UTI), sinusitis, cough/cold, pneumonia, skin infection, otitis media), and primary care prescriptions for antibiotics between 2-52 weeks before index, and for 2-156 weeks for patients with at least 3 years of prior observation. The Charlson comorbidity score[25]

was calculated, a weighted score of individual comorbidities, where a higher score indicates higher levels of comorbidity. This score was grouped as 0, 1-2, 3-4, 5-6 and 7+.

Any antibiotics prescribed within two weeks of the patient's index date were excluded, as they were considered potentially as part of the developing sepsis. Sensitivity analyses including these prescriptions were conducted (see Table S4.8). See thesis appendix for Read codes used to identify comorbidities and antibiotic prescriptions.

Summary statistics were created for the cohort and sub-cohorts. Continuous variables (age, BMI and Charlson comorbidity score) were reported as median with interquartile range, and also grouped to show the distribution. All discrete variables were reported as the number of patients and %. Differences in proportions of categorical variables were tested using Chi-squared tests and differences in continuous variables with Wilcoxon rank-sum tests.

Conditional logistic regression modelling was used, with development of sepsis as the binary outcome (0 for controls, 1 for cases). The following variables were included in unadjusted and adjusted models: prior antibiotic use, IMD quintile, BMI, smoking status, cancer, CVD, COPD, heart failure, dementia, diabetes, HIV, liver disease, moderate/severe renal disease, PVD, autoimmune disease, CHD, skin ulcers, hypertension and DVT. The individual comorbidity variables were selected as they have previously been assessed as potential risk factors for sepsis in other studies. We did not use any statistical method to select variables for the model (e.g. backward selection), due to the large sample size. A separate unadjusted model was run with Charlson comorbidity score as the covariate of interest, to assess whether overall levels of comorbidity also increased risk of sepsis. Prior infection consultations were not included in the model due to correlation with the number of antibiotic prescriptions. Age, sex and GP practice were not included in the model as they were used as variables to match controls to cases.

The models were run separately in the community- and hospital- acquired sepsis groups, and in the full cohort of patients with at least one year of prior-follow up and sub-cohort of patients with 3 years of follow-up (results in supplementary materials). Coefficients from the model were reported as odds ratios with 95% confidence intervals (CIs) and p-values with a significance threshold of 0.05.

For continuous variables where there were missing data (BMI), the missing values were set to 0 and a missing indicator variable created, where 0 denoted a recorded value, and 1 denoted a missing value. For categorical variables with missing data present (smoking status and IMD score) a separate missing level was created within the variable.

All analyses were performed in R, version 4.0.2. Particular packages used were *MatchIt* (case-control matching), *Survival* (conditional logistic regression model) and *tidyverse*.

The results presented are for both patient cohorts together (Gold and Aurum), for separate results please Tables S4.12-S4.14 in the supplementary materials.

4.4 Results

Out of a total of 55,346,914 patients in the Gold and Aurum source files there were 44,665,523 (80.7%) eligible for linkage to HES records. There were 245,109 patients aged >65 identified in HES records with an admission for sepsis. For patients with more than one sepsis admission the earliest admission was identified as the index episode. Figure 2, below, shows the exclusion criteria applied, leaving a total of 120,580 patients. After matching, a total of 705,959 eligible controls were found. 206 (0.17%) sepsis cases were excluded for whom there were no eligible controls, leaving a final case count of 120,374.

110,833 (92.1%) patients had 6 eligible controls (see Table S4.1). For the community-acquired sepsis patients there were a total of 640,932 eligible controls found, of whom 625,595 (97.6%) were registered at the same GP practice as their associated sepsis case and 363,364 (56.7%) who were the exact age in years as the sepsis case. In the hospital acquired sepsis control group there were only 28,143 (43.3%) controls who were matched exactly on age.

Of the final 120,374 sepsis cases, 109,069 (90.6%) were identified as having community-acquired sepsis and 11,305 (9.4%) with hospital-acquired sepsis. There were 104,078 cases (86.5%) who had 3 years of prior follow-up before their index date (see TableS4.5), with the other 16,296 cases (13.5%) having only one year of prior follow-up.

Table 1 below, shows the demographic and comorbidity breakdown for the cohorts. The median age of sepsis patients was 81 (IQR 74-87) with similar median age between community and hospital acquired sepsis patients (p-value 0.12). In the community cohort of sepsis patients there was a slightly higher proportion of females than males, with 55,650 (51.0%) females, but in the hospital sepsis group there was 5,657 (50.0%) females.

In terms of deprivation, there were 23,501 (21.6 %) community cases in the least deprived quintile, compared to 150,057 (23.8%) of controls (p-value <0.001), and in the most deprived quintile there were 19,482 (17.9%) cases compared to 101,880 (16.1%) controls (p-value <0.001). This was also similar in the sub groups of hospital patients.

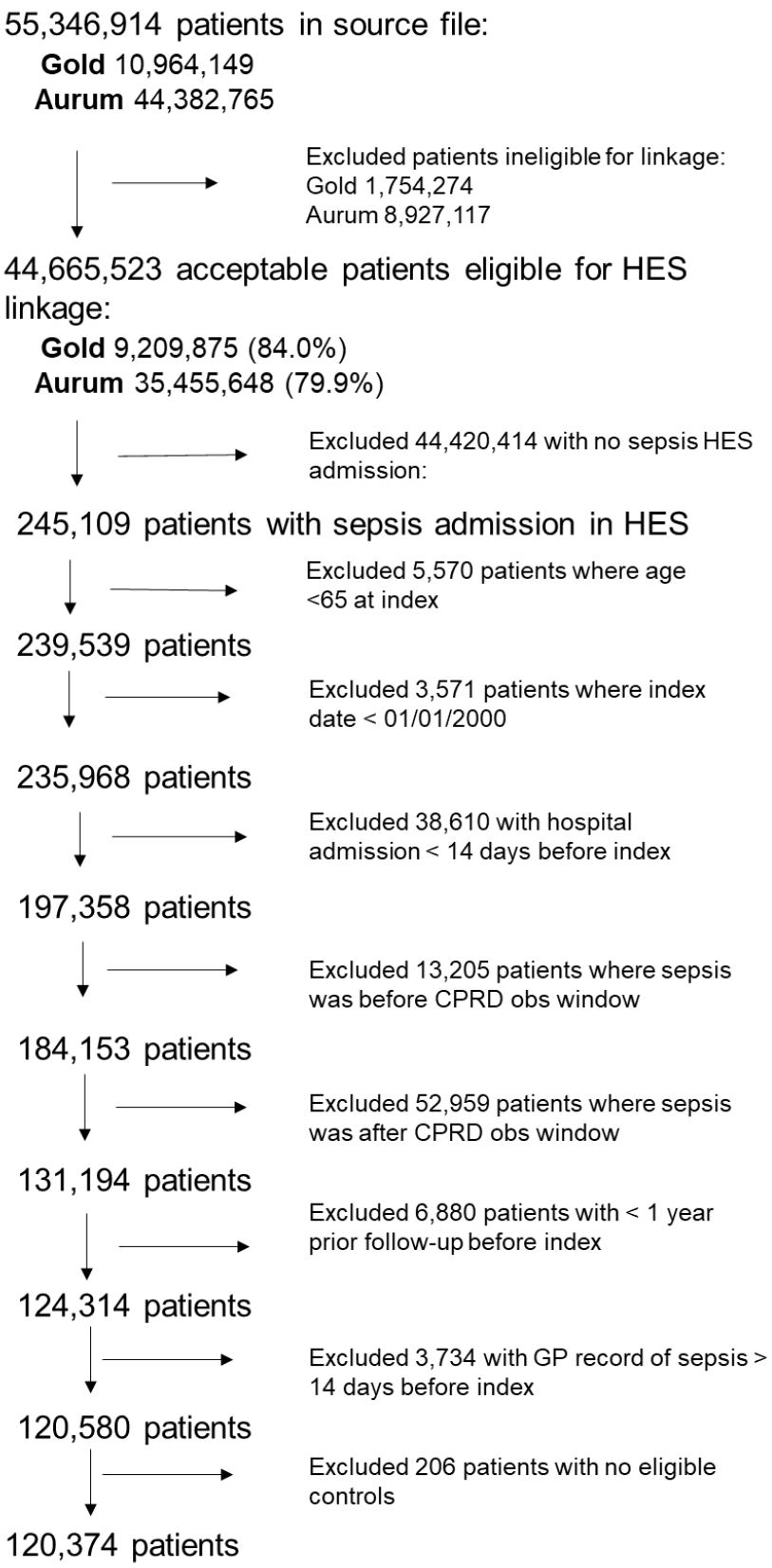


Figure 4.2 *Patient exclusion flowchart*

Exclusion flowchart for sepsis patients identified in HES records.

	Community Cohort			Hospital Cohort		
Variable	**Cases (n = 109,069)**	**Controls (n = 640,932)**	**p-value**	**Cases (n = 11,305)**	**Controls (n = 65,027)**	**p-value**
Gender, n female (%)	55,650 (51.0%)	327,329 (51.1%)	0.8	5,657 (50.0%)	32,676 (50.2%)	0.7
Ethnicity, n (%) White	92,373 (95.4%)	504,005 (95.1%)	<0.001	9,553 (95.2%)	55,289 (95.9%)	0.009
Black	1,381 (1.4%)	8,474 (1.6%)		181 (1.8%)	836 (1.4%)	
Asian	2,245 (2.3%)	12,507 (2.4%)		224 (2.2%)	1,128 (2.0%)	
Other	807 (0.8%)	5,095 (1.0%)		81 (0.8%)	415 (0.7%)	
Missing	12,263	110,851		1,266	7,359	
Age (years), median (IQR)	81.0 (74.0, 87.0)	81.0 (74.0, 87.0)	>0.9	81.0 (75.0, 87.0)	82.0 (75.0, 87.0)	<0.001
60-74	28,384 (26.0%)	165,652 (25.8%)	<0.001	2,766 (24.5%)	15,212 (23.4%)	0.002
75-84	42,094 (38.6%)	248,996 (38.8%)		4,562 (40.4%)	25,923 (39.9%)	
85-94	33,909 (31.1%)	200,321 (31.3%)		3,547 (31.4%)	21,058 (32.4%)	
>95	4,682 (4.3%)	25,963 (4.1%)		430 (3.8%)	2,834 (4.4%)	
BMI (kg/m^2), median (IQR)	26.9 (23.1, 30.1)	26.5 (23.4, 29.4)	<0.001	26.8 (23.0, 29.8)	26.6 (23.1, 29.5)	0.3
Low BMI (<18.5), n (%)	2,386 (4.5%)	9,146 (3.0%)	<0.001	240 (4.6%)	1,189 (3.9%)	0.003
Normal BMI (18.5-24), n (%)	17,450 (32.7%)	103,883 (34.3%)		1,727 (33.4%)	10,284 (33.9%)	
Overweight (25-30), n (%)	19,702 (36.9%)	123,627 (40.8%)		1,950 (37.7%)	11,970 (39.4%)	
Obese (>30), n (%)	13,892 (26.0%)	66,569 (22.0%)		1,260 (24.3%)	6,911 (22.8%)	
Missing, n	55,639	337,707		6,128	34,673	
Smoking status, n (%) Current	32,103 (47.0%)	172,859 (46.0%)	<0.001	3,331 (47.3%)	18,403 (45.3%)	0.008
Ex-smoker (1)	15,068 (22.1%)	79,361 (21.1%)		1,519 (21.6%)	9,048 (22.3%)	
Non-smoker (0)	21,082 (30.9%)	123,962 (33.0%)		2,193 (31.1%)	13,166 (32.4%)	
Missing	40,816	264,750		4,262	24,410	
IMD Quintile, n (%) 1 (least deprived)	23,501 (21.6%)	150,057 (23.8%)	<0.001	2,352 (20.9%)	14,740 (22.7%)	<0.001
2	23,326 (21.4%)	139,214 (22.1%)		2,335 (20.7%)	14,035 (21.6%)	
3	21,766 (20.0%)	125,812 (19.9%)		2,225 (19.7%)	13,611 (21.0%)	
4	20,809 (19.1%)	114,159 (18.1%)		2,175 (19.3%)	11,940 (18.4%)	
5 (most deprived)	19,482 (17.9%)	101,880 (16.1%)		2,188 (19.4%)	10,589 (16.3%)	
Missing	185	9,810		30	112	

Charlson comorbidity score, median (IQR)	2.0 (1.0, 4.0)	1.0 (0.0, 3.0)	<0.001	3.0 (1.0, 4.0)	2.0 (1.0, 4.0)	<0.001
0	17,688 (16.2%)	202,359 (31.6%)	<0.001	1,761 (15.6%)	10,425 (16.0%)	<0.001
1-2	38,339 (35.2%)	233,163 (36.4%)		3,890 (34.4%)	23,527 (36.2%)	
3-4	29,994 (27.5%)	134,625 (21.0%)		3,180 (28.1%)	17,857 (27.5%)	
5-6	14,672 (13.5%)	50,233 (7.8%)		1,615 (14.3%)	8,306 (12.8%)	
>7	8,376 (7.7%)	20,552 (3.2%)		859 (7.6%)	4,912 (7.6%)	
Comorbidity, n (%) Cancer	29,046 (26.6%)	116,303 (18.1%)	<0.001	2,899 (25.6%)	18,787 (28.9%)	<0.001
Cerebrovascular Disease	21,434 (19.7%)	90,444 (14.1%)	<0.001	2,384 (21.1%)	13,725 (21.1%)	>0.9
COPD	18,336 (16.8%)	87,696 (13.7%)	<0.001	1,883 (16.7%)	11,413 (17.6%)	0.021
Heart Failure	16,154 (14.8%)	55,278 (8.6%)	<0.001	1,896 (16.8%)	9,947 (15.3%)	<0.001
Dementia	13,267 (12.2%)	54,540 (8.5%)	<0.001	1,060 (9.4%)	5,430 (8.4%)	<0.001
Diabetes	27,325 (25.1%)	105,436 (16.5%)	<0.001	2,937 (26.0%)	13,948 (21.4%)	<0.001
HIV	8 (0.0%)	118 (0.0%)	0.013	1 (0.0%)	7 (0.0%)	>0.9
Liver Disease	1,264 (1.2%)	2,601 (0.4%)	<0.001	171 (1.5%)	632 (1.0%)	<0.001
Renal Disease	33,745 (30.9%)	150,834 (23.5%)	<0.001	3,708 (32.8%)	19,390 (29.8%)	<0.001
Peripheral Vascular Disease	10,850 (9.9%)	40,912 (6.4%)	<0.001	1,220 (10.8%)	6,567 (10.1%)	0.026
Autoimmune Disease	11,962 (11.0%)	46,807 (7.3%)	<0.001	1,260 (11.1%)	6,462 (9.9%)	<0.001
Deep Vein Thrombosis	1,259 (1.2%)	5,257 (0.8%)	<0.001	125 (1.1%)	745 (1.1%)	0.7
Skin Ulcer	14,094 (12.9%)	40,297 (6.3%)	<0.001	1,500 (13.3%)	6,333 (9.7%)	<0.001
Coronary Heart Disease	27,289 (25.0%)	129,756 (20.2%)	<0.001	3,031 (26.8%)	19,661 (30.2%)	<0.001
Hypertension	63,718 (58.4%)	345,593 (53.9%)	<0.001	6,732 (59.5%)	38,100 (58.6%)	0.058

Table 4.1 *Demographics and comorbidities of the cohort*

p-values represent differences between cases and controls within each cohort, for continuous variables derived from Wilcoxon rank sum, for categorical variables from Chi-square tests.

In the community cohort there was a higher proportion of controls with a Charlson score of 0 than cases (31.6% vs 16.2%, p-value <0.001), and a Charlson score of 1 or 2 (controls 36.4% vs cases 35.2%, p-value <0.001) but a higher proportion of cases with a Charlson score of 3 or more than controls (cases 48.6% vs controls 32.0%, p-value <0.001). However, for the hospital matched patients there was a similar proportion of controls than cases with 0 comorbidities (controls 16.0% vs cases 15.6%, p-value 0.229), a Charlson score of 3-4 (controls 27.5% vs cases 28.1%, p-value 0.145) and 7+ (controls 7.6% vs cases 7.6%, p-value 0.884).

In terms of specific comorbidities, there was a higher prevalence of all comorbidities in the cases in the community cohort than in the matched control group. There was a high prevalence of hypertension in both the case and control groups, affecting 63,718 (58.4%) cases and 345,593 (53.9%) controls (p-value <0.001). Along with hypertension the most common comorbidities in the community sepsis case group were cancer (29,046 patients, 26.6%), diabetes (type 1 and 2, 27,325 patients, 25.1%), renal disease (33,745 patients, 30.9%) and coronary heart disease (27,289 patients, 25.0%).

For the hospital cohort, there was similar prevalence between the cases and controls with some of the comorbidities having a higher prevalence in the control group than the case group (cancer 28.9% vs 25.6%, p-value <0.001, COPD 17.6% vs 16.7%, p-value 0.021 and coronary heart disease 30.2% vs 26.8%, p-value <0.001).

Figure 3 below shows the results from the fully adjusted conditional logistic regression model for the sub-groups of community and hospital patients (see Table S4.6 for p-value and odds ratios and unadjusted model results). Compared with patients who have never smoked, being a current smoker was associated with a slightly greater risk of sepsis in the community group (current OR 1.09, 95% CI 1.07-1.12, p-value <0.001), and hospital group (current OR 1.10 95% CI 1.03-1.17, p-value <0.001).

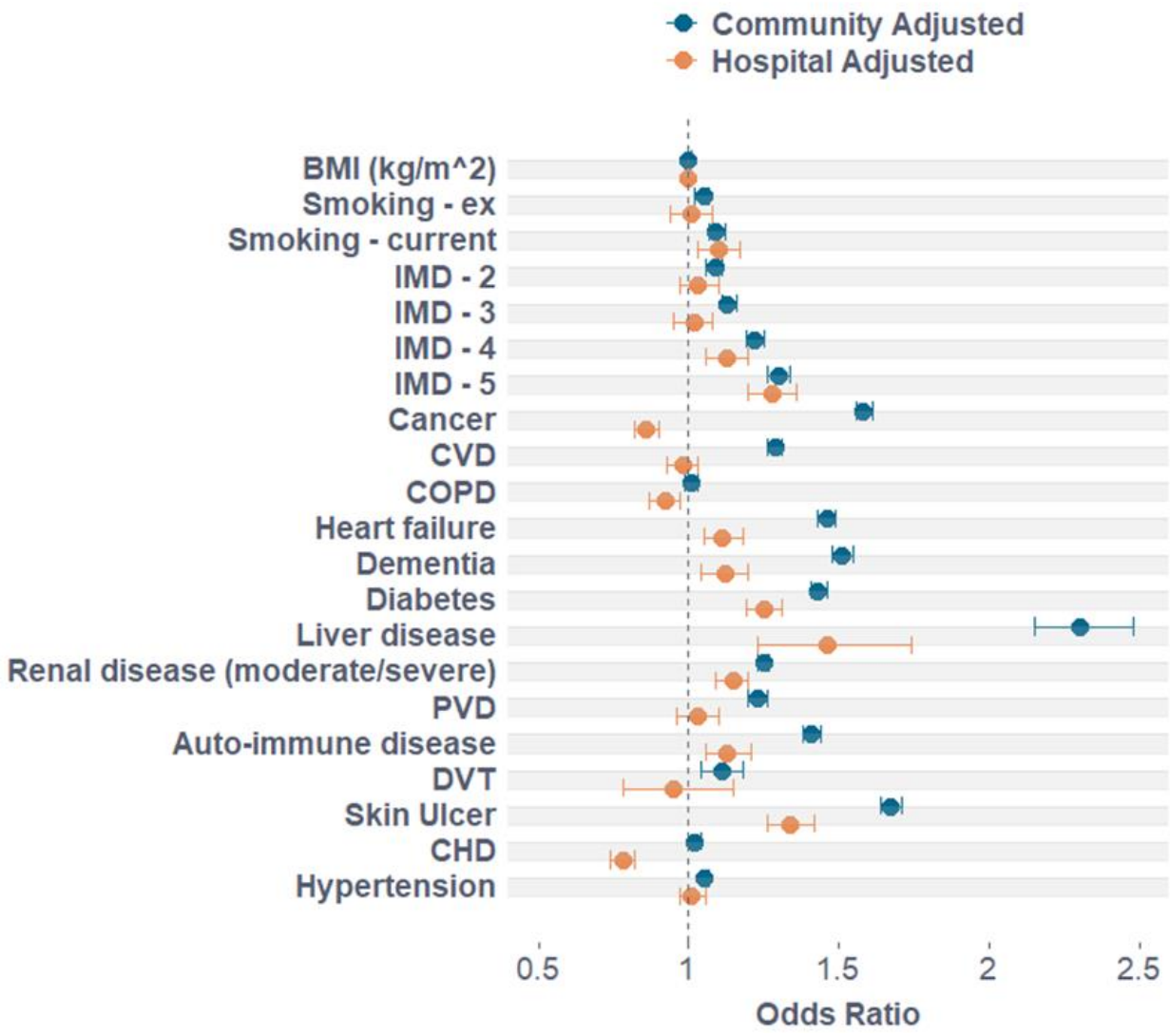


Figure 4.3 ***Fully adjusted conditional logistic model results for demographic and comorbidity variables***

Demographic and comorbidity variables only, data shown are odds ratios for development of sepsis with 95% confidence intervals for community patients (blue) and hospital patients (yellow). Results are from a fully adjusted conditional logistic regression model. Odds ratio for HIV not shown, community OR 0.38, 95% CI 0.18-0.79, hospital OR 0.96, 95% CI 0.12-7.82.

In terms of deprivation patients in the more deprived quintiles had a higher risk of sepsis than those in the least deprived quintile, with an OR of 1.30 (95% CI 1.26-1.34, p-value <0.001) for community patients in the 5th quintile, and an OR of 1.28 (95% CI 1.20-1.36, p-value <0.001) for hospital patients.

Looking at the comorbidities in community patients liver disease (OR 2.30, 95% CI 2.15-2.48, p-value <0.001), skin ulcers (OR 1.67, 95% CI 1.64-1.71, p-value <0.001), cancer (OR 1.58, 95% CI 1.56-1.61, p-value <0.001) and dementia (OR 1.51, 95% CI 1.48-1.55, p-value <0.001) were associated with the largest increased risk of developing sepsis. In the hospital cohort only liver disease (OR 1.46, 95% CI 1.23-1.74, p-value <0.001), skin ulcers (OR 1.34, 95% CI 1.26-1.42, p-value <0.001), diabetes (OR 1.25, 95% CI 1.19-1.31, p-value <0.001), heart failure (OR 1.11, 95% CI 1.05-1.18, p-value <0.001), renal disease (OR 1.15, 95% CI 1.09-1.20, p-value <0.001), and auto-immune disease (OR 1.13, 95% CI 1.16-1.21, p-value <0.001) were associated with an increased risk of sepsis. Cancer (OR 0.86, 95% CI 0.82-0.90, p-value <0.001), COPD (OR 0.92, 95% CI 0.87-0.97, p-value 0.002) and CHD (OR 0.78, 95% CI 0.74-0.82, p-value <0.001) were associated with a lower risk of sepsis in the hospital patients.

Figure 4 below, shows the results of an unadjusted logistic regression model with Charlson comorbidity score as the covariate of interest. Compared with patients with a Charlson comorbidity score of 0, patients with increasing levels of comorbidities had an increased risk of sepsis in the community cohort (1-2: OR 2.02, 95% CI 1.98-2.06, p-value <0.001, 3-4: OR 2.91, 95% CI 2.85-2.97, p-value <0.001, 5-6: OR 3.96, 95% CI 3.86-4.06, p-value <0.001, 7+: OR 5.57, 95% CI 5.40-5.75, p-value <0.001), but in the hospital cohort the effects were much lower (1-2: OR 0.99, 95% CI 0.93-01.05, p-value 0.7, 3-4: OR 1.07, 95% CI 1.01-1.15, p-value 0.029, 5-6: OR 1.18, 95% CI 1.09-1.27, p-value <0.001, 7+: OR 1.06, 95% CI 0.97-1.17, p-value 0.2). For full results Table S4.2.

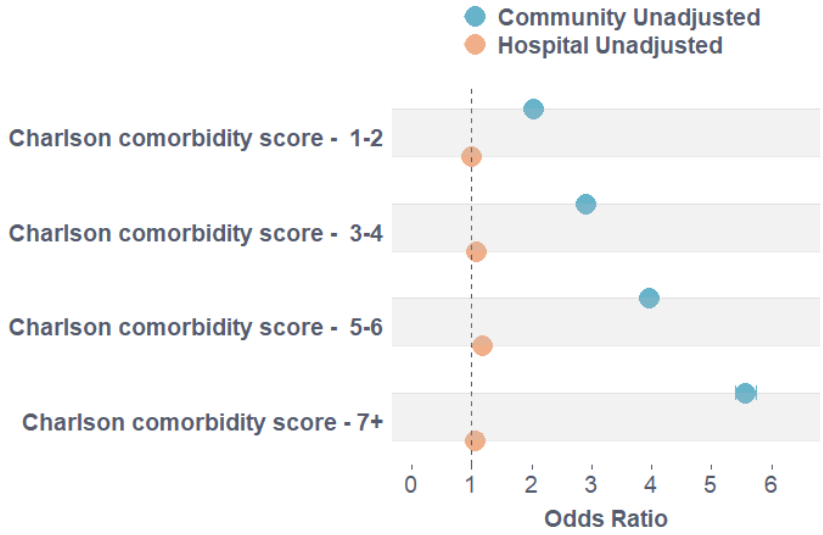


Figure 4.4 *Unadjusted conditional logistic model results for Charlson comorbidity score*

Charlson comorbidity score variable only, data shown are odds ratios for development of sepsis with 95% confidence intervals for community patients (blue) and hospital patients (yellow). Odds ratios and p-values are in supplementary materials.

There was 1,151,746 prescriptions (for 462,534 (56.0%) patients) for an antibiotic in the 1 year before their index date (not including those within 2 weeks of index). Of those, 455,390 (39.5%) were broad-spectrum antibiotics (see Table S4.3). Amoxicillin was the most frequently prescribed, accounting for 251,515 (21.8%) of prescriptions, followed by Trimethoprim (163,454 – 14.2%), Flucloxacillin (128,610 – 11.2%), Nitrofurantoin (107,748 – 9.4%) and Doxycycline (85,150 – 7.4%). There were 65,681 community cases (60.2%) and 255,873 (39.9%) controls with at least 1 antibiotic prescription, however, in the hospital patients there was 6,509 cases (57.6%) and 35,736 (55.0%) controls with prescriptions. There was a greater proportion of cases in the community cohort in the higher prescribing groups than controls (5-6 prescriptions 6.1% vs 2.8%, p-value <0.001; 7+ prescriptions 8.0% vs 3.4%, p-value <0.001). In the hospital cohort there were still more cases than controls, however the difference was less (5-6 prescriptions 5.3% vs 4.8%, p-value 0.015; 7+ prescriptions 7.0% vs 6.1%, p-value <0.001). Figure 5 below shows the number of prescriptions per patient in the 1 year prior to index (not including those within 2 weeks of index).

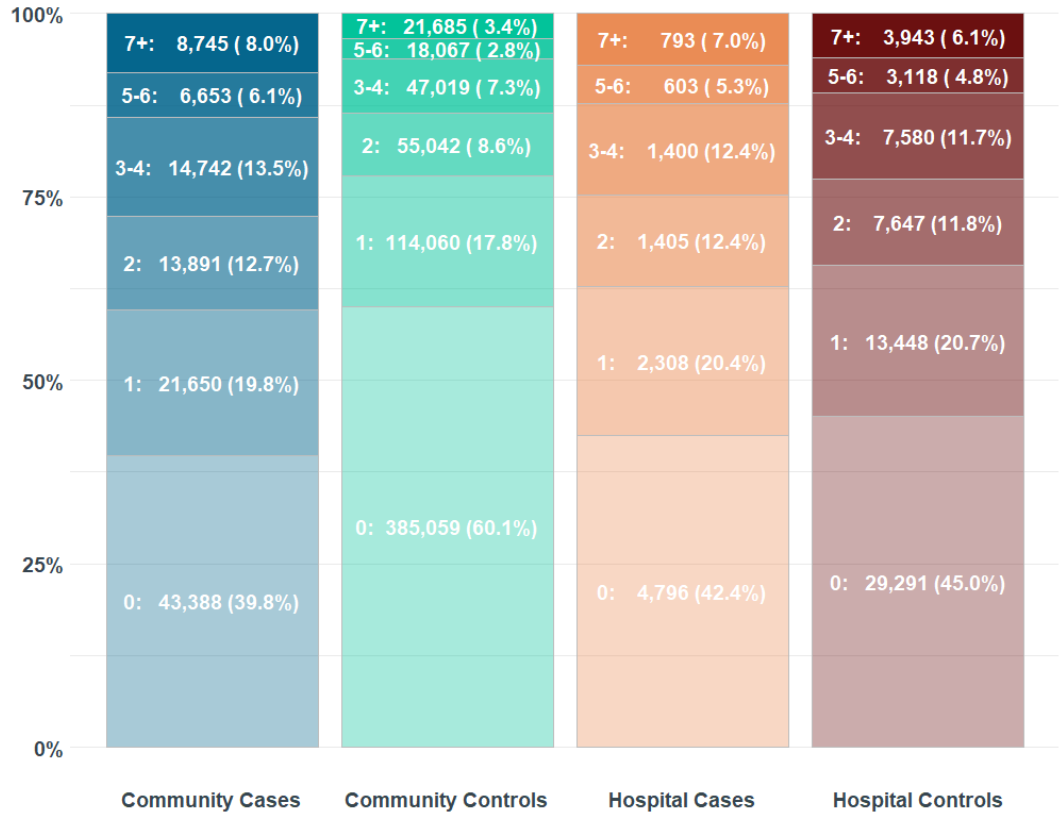


Figure 4.5 *Number of antibiotics prescribed per patient in the one year prior to index*

Does not include prescriptions within two weeks of index. All differences between the community cases and control were significant (p-value <0.001). For the hospital group, 0 antibiotic p-value <0.001, 1 antibiotic p-value 0.529, 2 antibiotics p-value 0.044, 3-4 antibiotics 0.028, 5-6 antibiotics 0.015, 7+ antibiotics <0.001

In terms of antibiotic use (Figure 6) for patients in the community cohort, compared to patients who did not receive any antibiotics in the year prior to index patients who received 1 (OR 1.57, 95% CI 1.54-1.60, p-value <0.001), 2 (OR 2.02, 95% CI 1.97-2.06, p-value <0.001), 3-4 (OR 2.42, 95% CI 2.36-2.47, p-value <0.001), 5-6 (OR 2.75, 95% CI 2.67-2.84, p-value <0.001) or more than 7 (OR 2.98, 95% CI 2.89-3.07, p-value <0.001) prescriptions were at an increased risk of developing sepsis. For the hospital sepsis patients, however, there was a much weaker association (1: OR 1.04, 95% CI 0.98-1.10, p-value 0.2, 2: OR 1.10, 95% CI 1.03-1.18, p-value 0.003, 3-4: OR 1.10, 95% CI 1.03-1.18, p-value 0.005, 5-6: OR 1.15, 95% CI 1.04-1.26, p-value 0.004, 7+: OR 1.19, 95% CI 1.09-1.29, p-value <0.001).

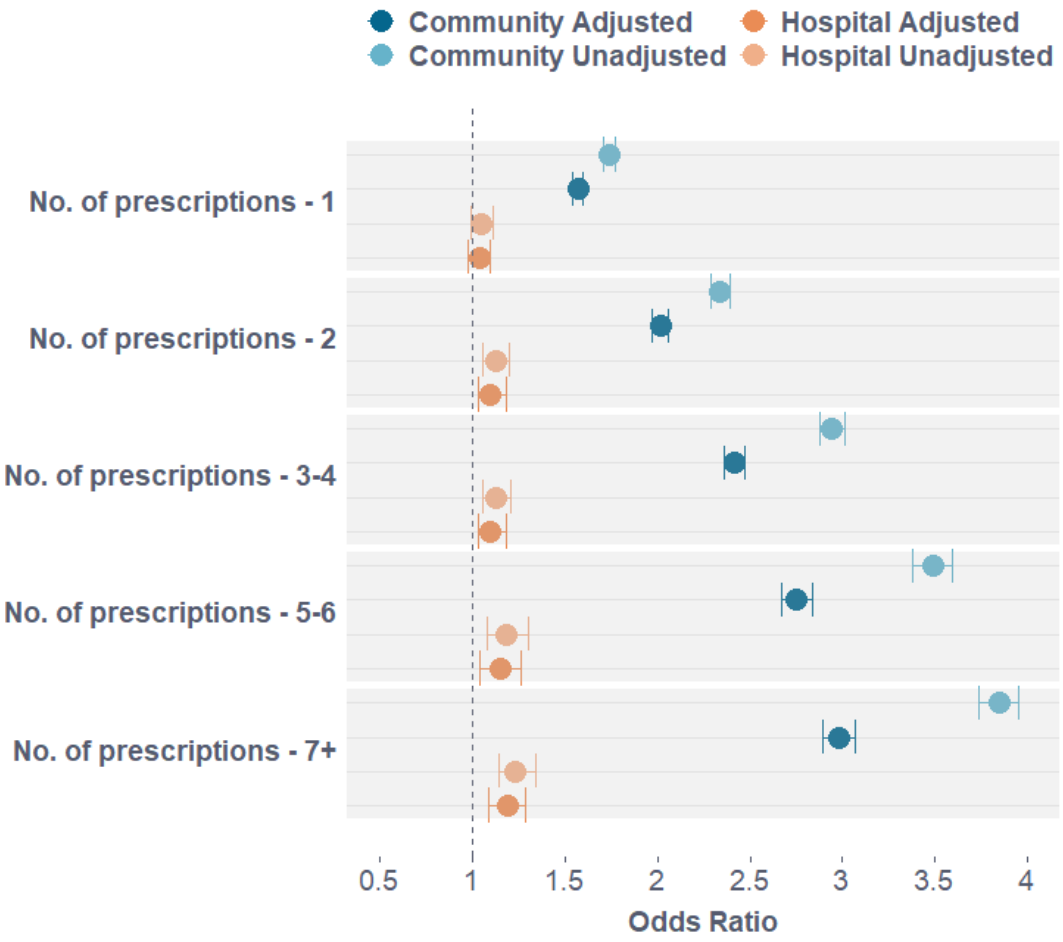


Figure 4.6 *Unadjusted and adjusted conditional logistic model results for antibiotic use*

Prior antibiotic use only, data shown are odds ratios for developing sepsis with 95% confidence intervals for community patients (blue) and hospital patients (yellow). All odds ratios and p-values are in TableS4.

The model results (un-adjusted and adjusted) for the sub-cohorts of patients who have at least three years of prior follow-up prior to index are shown in the supplementary materials (Table S4.7). There was not much difference in the reported odds ratios for the demographic and

comorbidity covariates, across the hospital and community patients. For community patients those who had received more antibiotics were at a higher risk of sepsis (12+: OR 2.95, 95% CI 2.86-3.03, p-value <0.001), but not for hospital patients (12+: OR 1.07, 95% CI 0.98-1.17, p-value 0.12).

There was a total of 894,039 GP consults for common infections in the year leading up to the patient's index dates (not including consults within the two weeks immediately prior to index, see Table S4.3), for 335,607 patients (40.6%). The most frequent indication was for infections linked to asthma & COPD, accounting for 169,803 consultations (19.0%), followed by urinary tract infections (154,092 – 17.2%), coughs & colds (146,714 – 16.4%), skin infections (145,939 – 16.3%) and lower respiratory tract infections (134,725 – 15.1%). Similar to the pattern of antibiotic prescribing there was a bigger difference in the number of cases and controls with infection consultations in the community group (cases 59.2% vs controls 36.4%) than in the hospital group (51.7% vs 49.1%). When looking at the consults for common infection within the two weeks immediately prior to the index date (see Table 3 below), there were 26,441 community cases (24.2%) with a consult, compared with only 23,022 (6.8%) controls. In the hospital patients there was a lower proportion of cases (12.4%) with a consult than in the community group, however there was a higher proportion of controls (7.7%). The incidence of antibiotic prescriptions in that same two week window is 21,181 community cases (19.4%) and 1,178 hospital cases (10.4%) receiving an antibiotic, compared to 31,054 (4.8%) of community controls and 5,508 (8.5%) hospital controls.

Patients who developed sepsis in the hospital (>2 days after admission) were in hospital for a median of 7 days (IQR 4-14) prior to their index date. After their index dates, community sepsis patients had a median length of stay in hospital of 11 days (IQR 5-24), whereas the hospital sepsis patients had longer lengths of stay of 21 days (IQR 10-43). The proportion of hospital sepsis patients requiring a period of either augmented or critical care during their hospital stay was higher than the community sepsis cases, with 1,944 (17.2%) hospital cases vs community cases 12,173 (11.7%). In terms of in-hospital mortality, the mortality rate was 46.3% for hospital sepsis cases compared to 34.4% for community sepsis.

	Community Cohort		Hospital Cohort	
	Cases (n = 109,069)	**Controls (n = 640,932)**	**Cases (n = 11,305)**	**Controls (n = 65,027)**
No. of consultations in 2 weeks prior to index	36,394	28,383	1,889	6,456
No. of patients with a consultation in 2 weeks prior to index (n, % of patients)	26,441 (24.2%)	23,022 (6.8%)	1,406 (12.4%)	4,980 (7.7%)
Types of infection most frequent (n, % of total infections within 2 weeks)				
1	UTI (8,149, 22.4%)	Asthma/COPD (5,173, 18.2%)	UTI (439, 23.2%)	UTI (1,466, 22.7%)
2	Sepsis (7,735, 21.3%)	Cough/cold (4,917, 17.3%)	LRTI (309, 16.4%)	LRTI (1,269, 19.7%)
3	LRTI (5,773, 15.9%)	UTI (4,873, 17.2%)	Sepsis (271, 14.3%)	Asthma/COPD (1,201, 18.6%)
4	Skin infection (3,982, 10.9%)	LRTI (4,642, 16.4%)	Skin infection (270, 14.3%)	Skin infection (832, 12.9%)
5	Pneumonia (3,479, 9.6%)	Skin infection (4,054, 14.3%)	Pneumonia (232, 12.3%)	Cough/cold (628, 9.7%)
No. of antibiotic prescriptions in 2 weeks prior to index	25,937	35,880	1,419	6,483
No. of patients with a prescription in 2 weeks prior to index (n, % of patients)	21,181 (19.4%)	31,054 (4.8%)	1,178 (10.4%)	5,508 (8.5%)

Table 4.2 *Primary care consultations for common infections and antibiotic use in the two weeks prior to index date*

UTI – urinary tract infection, LRTI – lower respiratory tract infection, COPD – chronic obstructive pulmonary disease

	Community Cohort	Hospital Cohort	
	Cases (n = 109,069)	**Cases (n = 11,305)**	**Controls (n = 65,027)**
Hospital length of stay after index (days, median (IQR))	11 (5, 24)	21 (10, 43)	9 (3, 21)
In-hospital mortality (n, %)	37,679 (37.9%)	5,230 (46.3%)	4,537 (7.0%)
No. of patients requiring critical or augmented care periods (n, %)	12,713 (11.7%)	1,944 (17.2%)	
Admission method (n, %)			
Emergency - via ED	83,957 (77.0%)	8,311 (73.5%)	31,487 (48.4%)
Emergency - via GP	14,586 (13.4%)	523 (4.6%)	21,698 (33.4%)
Emergency - other	5,006 (4.6%)	1,767 (15.6%)	6,873 (10.6%)
Elective	4,304 (3.9%)	543 (4.8%)	3,295 (5.1%)
Other	1,215 (1.1%)	161 (1.4%)	1,674 (2.6%)

Table 4.3 *Hospital length of stay, in-hospital mortality and admission method*

4.5 Discussion

4.5.1 Key findings

This study found that higher comorbidity levels and prior antibiotic prescribing was associated with an increased risk of community-acquired sepsis, while the effects were much smaller for hospital-acquired sepsis. Patients with hospital-acquired sepsis had a higher in-hospitality mortality rate, longer length of stay and a higher proportion of patients requiring critical/augmented care than community-acquired sepsis cases.

4.5.2 How do the findings fit in with existing literature?

The proportion of patients with community-acquired sepsis was moderately higher than in comparison to other studies (90.6%). However, this could be due to different criteria used. Jones et al[6] reported a rate of 85%, but they only classed community-acquired if patients had sepsis as they were admitted to hospital. In a study by Page et al[14] using a national US dataset, 11.3% of the patients were found to have hospital acquired sepsis, which they defined as patients who did not have any infection recorded on admission. Other studies who have used 48 hours as a cut-off point have reported community-acquired sepsis rates of 25%, 42% and 53%, respectively, however they were all looking at patients in ICU only, who were more severely ill[26–28]. In other studies patients who have hospital-acquired sepsis do have worse outcomes, in terms of mortality and severity of sepsis[14,29,30].

Other studies looking at overall comorbidity levels and specific conditions have found similar results in that chronic conditions such as diabetes, liver disease, kidney disease and heart failure increase the risk of community-acquired sepsis[31–33]. In our study we did not find a significant association between COPD and the risk of sepsis, which does contradict other studies that have found an association between chronic lung disease (including, but not limited to, COPD) and sepsis[31,32], but there were differences in the definitions used and methods of data collection, with both studies reporting a higher incidence than in our study. The only study available looking at comorbidities that differentiates between community and hospital acquired sepsis does not report the levels of comorbidities in the subgroups[7].

The differences in the association between comorbidities and risk of community-acquired sepsis and hospital-acquired sepsis suggest that other factors may be important in identifying patients at risk of hospital-acquired sepsis. Additionally, hospital-acquired sepsis patients also had higher in-hospital mortality and length of stay, highlighting further differences between

them and community-acquired sepsis patients. Factors relating to their hospital admission such as the length of stay in hospital before developing sepsis, the initial diagnosis on hospital admission, whether they have undergone an invasive surgical procedure[34] or the type of infection/antibiotics used in-hospital could all potentially increase the risk of sepsis, by making patients vulnerable to healthcare-acquired infections and potentially exposing them to resistant strains[17].

The literature around the effects of antibiotics on reducing infection-related complications is limited, particularly with respect to incidental and repeated antibiotic uses. A study by van Bodegraven et al[18] looked at incidental antibiotic prescribing on a English general practice level, and found that lower levels of antibiotic prescribing was associated with higher levels of infection-related hospital admissions and complications. However, another study also using CPRD data found that practices with lower antibiotic prescribing had similar risks of serious bacterial infections compared to higher prescribing practices. This study did not use any hospital admissions data and only relied on GP records of infection[35]. Gharbi et al[36] looked at incidence of blood stream infections (BSI) and all-cause mortality after a consultation for a UTI in elderly patients in England. Those who did not receive an antibiotic or had a deferred antibiotic were at higher risk of BSI and death than those who were prescribed an antibiotic immediately. Neither of these studies, however, stratified according to prior history of antibiotic prescribing. There is also evidence that use of antibiotics increases the risk of developing antimicrobial resistance on an individual level[17,37,38]. The systematic review and meta-analysis by Costelloe et al concluded that patients treated with an antibiotic developed resistance to that antibiotic, and this resistance persisted for up to one year[17].

A study by van Staa et al[39], also using CPRD and HES data, showed that repeated antibiotic use in individual patients in primary care was associated with an increased risk of infection-related hospital admission. There is evidence of a link between the gut microbiome and sepsis[40], and antibiotics are known to disrupt the gut microbiome[41]. A US study looked at risk of sepsis within 90 days of hospital admission, and found that patients treated with certain antibiotics and higher number of different classes of antibiotics, associated with *C. difficile* infections were at greater risk of a readmission for sepsis[42]. While confounding cannot be excluded as a possible explanation for these findings, there is limited evidence that repeated antibiotic use is actually safe and effective, while evidence is accumulating of possible adverse effects. An editorial by Krockow et al looked at the issues and drivers of repeat antibiotic use and suggest strategies to reduce inappropriate repeat prescriptions, as this is an important area to address in the efforts to reduce overall antibiotic prescriptions[43].

4.5.3 Strengths & Limitations

A strength of the study is the use of two large, national databases, covering a large proportion of the English population, and considered to be broadly representative. We were able to use linked primary and secondary care data, and identify patients with sepsis in secondary care data. This is potentially more accurate than identifying sepsis in primary care records as clinicians may be more experienced at recognising sepsis in secondary care. A study by Rezel-Potts in 2020[12] used CPRD Gold and HES records to look at how sepsis is recorded in GPs vs HES records and found that whilst the incidence of sepsis was similar when looking at either GP records or hospital data, the majority of patients with a hospital admission for sepsis did not also have a record in their GP data, and vice versa.

We also identified separate control groups for patients, depending on whether they had developed sepsis in the community or in hospital, which is the first study to use this approach. CPRD was used to identify population-based controls for community-acquired sepsis patients and HES records used to identify hospital admission controls for hospital-acquired sepsis patients. By using linked data we were able to extract primary care data for all patients, regardless of whether they were in the community or hospital cohort.

The use of population-based controls for the community-acquired sepsis could potentially mean that the increased risk associated with specific covariates could represent a greater risk of hospitalisation for any reason, not specifically sepsis. A 2014 study by Yende et al[44] assessing outcomes after a sepsis episode matched ICU sepsis patients with four different control patients, one population-based, one hospitalised without an infection, one hospitalised with an infection and another one admitted to ICU without severe sepsis. Similarly, a 2016 study identified three separate control groups for investigating mortality in sepsis, which were non-hospitalised patients, admitted patients with a non-sepsis diagnosis and patients admitted with an acute sterile inflammatory condition[45]. Therefore, an alternative approach in this study could have been to match patients to the same multiple control groups regardless of whether they had contracted sepsis in the community or hospital. This would help determine if the risk factors are specific to sepsis or severe illness in general.

A limitation of this study is the use of ICD-10 codes to identify sepsis. This has been shown to underestimate and overestimate the incidence of sepsis in different populations, compared to using clinical observations data and SIRS/ sepsis-3 criteria[46,47]. In this study data from patient's hospital stays was minimal, so using clinical data to identify patients was not possible.

Additionally, there are limitations around the classification of community- and hospital-acquired sepsis. There were no time stamps provided for start of admissions or episodes, only

dates, so we could only use the number of days, rather than hours, as a cut-off point. It was not possible to validate the dates provided so any errors in the dates could have led to some misclassification in the patient groups. This potentially could have affected the proportion of community- and hospital-acquired sepsis in the cohort induced a selection bias as the two groups were matched with different controls.

Another limitation is that prescriptions data was only available for primary care, not for the hospital admissions and also will not include antibiotic prescribing in dentists, walk-in services or emergency departments, but primary care does account for around 85% of prescribing. Additionally, microbiology data was not available for hospital admissions. For patients who developed sepsis in the hospital the type of infection they had and what antibiotics they were treated with prior to developing sepsis could be a potential risk factor.

A fourth limitation was that we excluded patients below the age of 65. This was largely due to the need to reduce the amount of data requested from CPRD, to avoid delays in extracting data and availability of pre-existing data extracts of patients in this age group. Both age and frailty have been shown to be associated with an increased risk of both developing sepsis and of worse outcomes[48–50] and previous studies have reported between 60 and 70% of their cohorts being over the age of 65[12,31]. By restricting our cohort based age we have potentially introduced bias towards patients who are at greater risk of sepsis than the general population, although we have matched cases to controls on age which should have minimised this. An alternative approach could have been to randomly sample patients from each age group, as in the paper by Gulliford et al[19].

There were additional potential comorbidity risk factors for sepsis not included in this study, such as pancreatitis, atrial fibrillation and hyperlipidaemia. Other factors such as vaccination status and immunocompromised status (other than related to autoimmune disease or cancer) through use of certain medications such as corticosteroids or biologics were also not included. The reason for this was mainly due to time constraints and the fact that we only had access to medications in primary care records, not secondary care. Some complex conditions may require treatments administered in hospital, not through the GP, which wouldn't be captured here. This does mean, however, that there may be residual unmeasured confounding not taken into account in these models. Future studies could look at the effect of these factors on the risk of sepsis.

A major issue around antibiotic prescribing is whether it is inappropriate or not, but this was not evaluated in this study. Other studies looking at appropriateness of prescribing have found that antibiotics are frequently prescribed without recorded codes for infection[51,52] in both CPRD and another UK GP database.

4.5.4 Conclusion

The aims of this study were to use a national database of linked electronic health record data to identify risk factors, including the potential role of antibiotics, for development of sepsis and to look at the differences in risk factors between community- and hospital-acquired sepsis patients. We found that higher levels of comorbidity and prior antibiotic prescribing was associated with increased risk of community-acquired sepsis but with much smaller effects in hospital-acquired sepsis. This suggests that the aetiologies of community- and hospital-acquired sepsis may be different.

Given the known effects of antibiotics on the host, its gut microbiome and downstream population effects due to resistance pressures, the regular practice of indiscriminately prescribing antibiotics repeatedly and intermittently should be discouraged, given their uncertain benefits and likely risks. Further work could develop a clinical prediction model that could identify patients in the community at greater risk of sepsis. This could be act as an early warning score for sepsis and help inform clinicians prescribing of antibiotics in primary care, at the point of prescribing.

4.6 References

1. Singer, M. *et al.* The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* **315**, 801 (2016).

2. Daniels, R. *et al. The Sepsis Manual*. (United Kingdom Sepsis Trust, 2017).

3. Liu, V. *et al.* Hospital readmission and healthcare utilization following sepsis in community settings. *J Hosp Med* **9**, 502–7 (2014).

4. Jones, T. K. *et al.* Post–Acute Care Use and Hospital Readmission after Sepsis. *Ann Am Thorac Soc* **12**, 904–913 (2015).

5. Shankar-Hari, M. & Rubenfeld, G. D. Understanding Long-Term Outcomes Following Sepsis: Implications and Challenges. *Curr Infect Dis Rep* **18**, (2016).

6. Jones, S. L. *et al.* Outcomes and resource use of sepsis-associated stays by presence on admission, severity, and hospital type. *Med Care* **54**, 303–310 (2016).

7. Novosad, S., Sapiano, M. & Grigg, C. Vital Signs: Epidemiology of Sepsis: Prevalence of Health Care Factors and Opportunities for Prevention. *Ann Emerg Med* **69**, 131–135 (2017).

8. Faisal, M. *et al.* Computer-aided National Early Warning Score to predict the risk of sepsis following emergency medical admission to hospital: a model development and external validation study. *Can Med Assoc J* **191**, E382–E389 (2019).

9. Scherpf, M., Gräßer, F., Malberg, H. & Zaunseder, S. Predicting sepsis with a recurrent neural network using the MIMIC III database. *Comput Biol Med* **113**, (2019).

10. Yee, C. R., Narain, N. R., Akmaev, V. R. & Vemulapalli, V. A Data-Driven Approach to Predicting Septic Shock in the Intensive Care Unit. (2019) doi:10.1177/1178222619885147.

11. Tavaré, A. & O'Flynn, N. Recognition, diagnosis, and early management of sepsis: NICE guideline. *Br J Gen Pract* **67**, 185–186 (2017).

12. Rezel-Potts, E. *et al.* Sepsis recording in primary care electronic health records, linked hospital episodes and mortality records: Population-based cohort study in England. *PLoS One* **15**, (2020).

13. Wang, H. E. *et al.* Chronic Medical Conditions and Risk of Sepsis. *PLoS One* **7**, 1–7 (2012).

14. Page, D. B., Donnelly, J. P. & Wang, H. E. Community-, Healthcare-, and Hospital-Acquired Severe Sepsis Hospitalizations in the University HealthSystem Consortium. *Crit Care Med* **43**, 1945–51 (2015).

15. van Vught, L. A. *et al.* Incidence, Risk Factors, and Attributable Mortality of Secondary Infections in the Intensive Care Unit After Admission for Sepsis. *JAMA* **315**, 1469 (2016).

16. Shallcross, L. J. & Davies, S. C. Antibiotic overuse: A key driver of antimicrobial resistance. *British Journal of General Practice* vol. 64 604–605 Preprint at https://doi.org/10.3399/bjgp14X682561 (2014).

17. Costelloe, C., Metcalfe, C., Lovering, A., Mant, D. & Hay, A. D. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: Systematic review and meta-analysis. *BMJ (Online)* **340**, 1120 (2010).

18. van Bodegraven, B. *et al.* Infection-related complications after common infection in association with new antibiotic prescribing in primary care: retrospective cohort study using linked electronic health records. *BMJ Open* **11**, e041218 (2021).

19. Gulliford, M. C. *et al.* Probability of sepsis after infection consultations in primary care in the United Kingdom in 2002-2017: Population-based cohort study and decision analytic model. *PLoS Med* **17**, e1003202 (2020).

20. Wolf, A. *et al.* Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. *Int J Epidemiol* **48**, 1740-1740G (2019).

21. CPRD. *Linkage Source Data Documentation (set 20)*. (2021).

22. Herrett, E. *et al.* Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* **44**, 827–836 (2015).

23. Herbert, A., Wijlaars, L., Zylbersztejn, A., Cromwell, D. & Hardelid, P. Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). *Int J Epidemiol* **46**, 1093 (2017).

24. UK Government. *The English Indices of Deprivation 2015*. *Department for Communities and Local Government* (2015).

25. Charlson, M. E., Pompei, P., Ales, K. L. & MacKenzie, C. R. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* **40**, 373–383 (1987).

26. Adrie, C. *et al.* Epidemiology and economic evaluation of severe sepsis in France: age, severity, infection site, and place of acquisition (community, hospital, or intensive care unit) as determinants of workload and cost. *J Crit Care* **20**, 46–58 (2005).

27. Sousa, C., Brandão, M., Ribeiro, O. & Cardoso, T. Community-Acquired Severe Sepsis: A Prospective Cohort Study. *Open Journal of Internal Medicine* **05**, 37–49 (2015).

28. Shah, A. D. *et al.* Descriptors of Sepsis Using the Sepsis-3 Criteria: A Cohort Study in Critical Care Units Within the U.K. National Institute for Health Research Critical Care Health Informatics Collaborative*. *Crit Care Med* **49**, 1883–1894 (2021).

29. Rothman, M. *et al.* Sepsis as 2 problems: Identifying sepsis at admission and predicting onset in the hospital using an electronic medical record–based acuity score. *J Crit Care* **38**, 237–244 (2017).

30. Tonai, M. *et al.* Hospital-onset sepsis and community-onset sepsis in critical care units in Japan: a retrospective cohort study based on a Japanese administrative claims database. *Crit Care* **26**, 1–9 (2022).

31. Wang, H. E. *et al.* Chronic Medical Conditions and Risk of Sepsis. *PLoS One* **7**, (2012).

32. Henriksen, D. P. *et al.* Risk Factors for Hospitalization Due to Community-Acquired Sepsis – A Population-Based Case-Control Study. *PLoS One* **10**, e0124838 (2015).

33. Costantini, E., Carlin, M., Porta, M. & Brizzi, M. F. Type 2 diabetes mellitus and sepsis: state of the art, certainties and missing evidence. *Acta Diabetol* **1**, 3 (2021).

34. Hotchkiss, R. S. *et al.* Sepsis and septic shock. *Nat Rev Dis Primers* **2**, 16045 (2016).

35. Gulliford, M. C. *et al.* Serious bacterial infections and antibiotic prescribing in primary care: cohort study using electronic health records in the UK. *BMJ Open* **10**, e036975 (2020).

36. Gharbi, M. *et al.* Antibiotic management of urinary tract infection in elderly patients in primary care and its association with bloodstream infections and all cause mortality: population based cohort study. *BMJ* **364**, l525 (2019).

37. Stracy, M. *et al.* Minimizing treatment-induced emergence of antibiotic resistance in bacterial infections. *Science* **375**, 889–894 (2022).

38. Yelin, I. *et al.* Personal clinical history predicts antibiotic resistance of urinary tract infections. *Nat Med* **25**, 1143–1152 (2019).

39. Van Staa, T. P. *et al.* The effectiveness of frequent antibiotic use in reducing the risk of infection-related hospital admissions: Results from two large population-based cohorts. *BMC Med* **18**, 1–11 (2020).

40. Adelman, M. W. *et al.* The gut microbiome's role in the development, maintenance, and outcomes of sepsis. *Crit Care* **24**, 1–10 (2020).

41. Ramirez, J. *et al.* Antibiotics as Major Disruptors of Gut Microbiota. *Front Cell Infect Microbiol* **10**, (2020).

42. Baggs, J. *et al.* Risk of Subsequent Sepsis within 90 Days of a Previous Hospital Stay by Type of Antibiotic Exposure. *Clin Infect Dis* **66**, 1004 (2018).

43. Krockow, E. M., Harvey, E. J. & Ashiru-Oredope, D. Addressing long-term and repeat antibiotic prescriptions in primary care: considerations for a behavioural approach. *BMJ Qual Saf* **0**, 1–5 (2022).

44. Yende, S. *et al.* Risk of cardiovascular events in survivors of severe sepsis. *Am J Respir Crit Care Med* **189**, 1065–1074 (2014).

45. Prescott, H. C., Osterholzer, J. J., Langa, K. M., Angus, D. C. & Iwashyna, T. J. Late mortality after sepsis: propensity matched cohort study. *BMJ* **353**, i2375 (2016).

46. Mariansdatter, S. E., Eiset, A. H., Søgaard, K. K. & Christiansen, C. F. Differences in reported sepsis incidence according to study design: a literature review. *BMC Med Res Methodol* **16**, 1–13 (2016).

47. Wilhelms, S. B., Huss, F. R., Granath, G. & Sjöberg, F. Assessment of incidence of severe sepsis in Sweden using different ways of abstracting International Classification of Diseases codes: Difficulties with methods and interpretation of results. *Crit Care Med* **38**, 1442–1449 (2010).

48. Lee, H. Y. *et al.* Preexisting Clinical Frailty Is Associated With Worse Clinical Outcomes in Patients With Sepsis. *Crit Care Med* **Publish Ah**, (2021).

49. Mahalingam, M., Moore, J. X., Donnelly, J. P., Safford, M. M. & Wang, H. E. Frailty Syndrome and Risk of Sepsis in the REasons for Geographic And Racial Differences in Stroke (REGARDS) Cohort. *J Intensive Care Med* **34**, 292–300 (2019).

50. Martin, G. S., Mannino, D. M. & Moss, M. The effect of age on the development and outcome of adult sepsis. *Crit Care Med* **34**, 15–21 (2006).

51. Sun, X. & Gulliford, M. C. Reducing antibiotic prescribing in primary care in England from 2014 to 2017: Population-based cohort study. *BMJ Open* **9**, (2019).

52. Dolk, F. C. K., Pouwels, K. B., Smith, D. R. M., Robotham, J. V & Smieszek, T. Antibiotics in primary care in England: which antibiotics are prescribed and for which conditions? *Journal of Antimicrobial Chemotherapy* **73**, ii2–ii10 (2017).

4.7 Supplementary Materials

Number of Controls	Number of Cases		
	Full Cohort	**Community Cohort**	**Hospital Cohort**
1	390 (0.3%)	280 (0.3%)	110 (1.0%)
2	603 (0.5%)	433 (0.4%)	170 (1.5%)
3	873 (0.7%)	685 (0.6%)	188 (1.7%)
4	1,629 (1.4%)	1,373 (1.3%)	256 (2.3%)
5	6,046 (5.0%)	5,549 (5.1%)	497 (4.4%)
6	110,833 (92.1%)	100,749 (92.4%)	10,084 (89.2%)

Table S4.1 ***Summary of sepsis patients and the number of eligible controls found after case-control matching***

		Community Cohort (1yr)			Hospital Cohort (1yr)		
Covariate		OR	95% CI	p-value	OR	95% CI	p-value
Charlson comorbidity score	1-2	2.02	1.98, 2.06	<0.001	0.99	0.93, 1.05	0.7
	3-4	2.91	2.85, 2.97	<0.001	1.07	1.01, 1.15	0.029
	5-6	3.96	3.86, 4.06	<0.001	1.18	1.09, 1.27	<0.001
	7+	5.57	5.40, 5.75	<0.001	1.06	0.97, 1.17	0.2

Table S4.2 *Charlson comorbidity score unadjusted odds ratios for conditional logistic regression model for patients with at least 1 year of prior follow-up*

	Community Cohort		Hospital Cohort	
	Cases (n = 109,069)	**Controls (n = 640,932)**	**Cases (n = 11,305)**	**Controls (n = 65,027)**
Number of patients with no antibiotic prescriptions (n, %)	43,388 (39.8%)	385,059 (60.0%)	4,796 (42.4%)	29,291 (45.0%)
Number of patients with at least 1 antibiotic prescription (n, %)	65,681 (60.2%)	255,873 (39.9%)	6,509 (57.6%)	35,736 (55.0%)
Number of prescriptions				
Total (n)	247,093	758,891	23,182	122,580
Broad spectrum (n, % of total)	93,863 (38.0%)	303,879 (40.0%)	8,960 (38.7%)	48,688 (39.7%)
Types of antibiotics most frequent (n, % of total)				
Amoxicillin	46,905 (19.0%)	174,763 (23.0%)	4,445 (19.2%)	25,402 (20.7%)
Trimethoprim	34,671 (14.0%)	109,056 (14.4%)	3,003 (13.0%)	16,724 (13.6%)
Flucloxacillin	30,789 (12.5%)	81,130 (10.7%)	3,194 (13.8%)	13,497 (11.0%)
Nitrofurantoin	23,361 (9.5%)	72,080 (9.5%)	1,927 (8.3%)	10,380 (8.5%)
Doxycycline	17,764 (7.2%)	56,633 (7.5%)	1,598 (6.9%)	9,155 (7.5%)

Table S4.3 *Summary of primary care antibiotic use in the 1 year prior to index*

Not including prescriptions within two weeks of index.

	Community Cohort		Hospital Cohort	
	Cases (n = 109,069)	**Controls (n = 640,932)**	**Cases (n = 11,305)**	**Controls (n = 65,027)**
Number of patients with no infection consult (n, %)	44,498 (40.8%)	407,681 (63.6%)	5,455 (48.3%)	33,092 (50.9%)
Number of patients with at least 1 infection consult (n, %)	64,571 (59.2%)	233,251 (36.4%)	5,850 (51.7%)	31,935 (49.1%)
Number of infection consultations total (n)	247,093	758,891	23,182	122,580
Types of infections most frequent (n, % of total)				
Asthma/COPD	31,285 (17.6%)	115,005 (19.0%)	3,038 (18.2%)	20,475 (21.6%)
UTI	34,815 (19.6%)	99,968 (16.5%)	2,982 (17.9%)	16,327 (17.2%)
Cough/cold	25,133 (14.2%)	105,528 (17.4%)	2,212 (13.3%)	13,841 (14.6%)
Skin infection	35,157 (19.8%)	91,775 (15.2%)	3,457 (20.7%)	15,550 (16.4%)
LRTI	27,019 (15.2%)	90,758 (15.0%)	2,564 (15.4%)	14,384 (15.2%)

Table S4.4 *Summary of primary care consultations for common infections in the 1 year prior to index*

Not including consultations within two weeks of index.

		Community Cohort		Hospital Cohort	
Variable		**Cases (n = 94,057)**	**Controls (n = 553,507)**	**Cases (n = 10,021)**	**Controls (n = 58,852)**
Gender, n female (%)		47,431 (50.4%)	279,357 (50.5%)	4,967 (49.6%)	29,292 (49.8%)
Ethnicity, n (%)	White	79,132 (95.5%)	436,689 (95.2%)	8,417 (95.2%)	50,379 (95.8%)
	Black	1,135 (1.4%)	7,268 (1.6%)	159 (1.8%)	774 (1.5%)
	Asian	1,899 (2.3%)	10,697 (2.3%)	199 (2.3%)	1,047 (2.0%)
	Other	656 (0.8%)	4,268 (0.9%)	66 (0.7%)	379 (0.7%)
	Missing	11,235	94,585	1,180	6,273
Age (years), median (IQR)		81.0 (74.0, 87.0)	81.0 (74.0, 87.0)	81.0 (75.0, 87.0)	81.0 (75.0, 87.0)
	60-74	24,798 (26.4%)	144,943 (26.2%)	2,477 (24.7%)	13,906 (23.6%)
	75-84	36,479 (38.8%)	215,722 (39.0%)	4,055 (40.5%)	23,555 (40.0%)
	85-94	28,855 (30.7%)	170,949 (30.9%)	3,109 (31.0%)	18,859 (32.0%)
	>95	3,925 (4.2%)	21,893 (4.0%)	380 (3.8%)	2,532 (4.3%)
BMI (kg/m^2), median (IQR)		27.0 (23.2, 30.3)	26.6 (23.4, 29.4)	26.9 (23.0, 29.8)	26.6 (23.1, 29.5)
	Low BMI (<18.5), n (%)	2,010 (4.2%)	7,621 (2.9%)	206 (4.4%)	1,096 (3.9%)
	Normal BMI (18.5-24), n (%)	15,178 (31.9%)	90,029 (33.8%)	1,550 (33.1%)	9,370 (33.6%)
	Overweight (25-30), n (%)	17,731 (37.3%)	109,522 (41.1%)	1,764 (37.7%)	11,016 (39.5%)
	Obese (>30), n (%)	12,596 (26.5%)	59,547 (22.3%)	1,158 (24.8%)	6,408 (23.0%)
	Missing, n	46,542	286,788	5,343	30,962
Smoking status, n (%)	Current	29,276 (48.6%)	156,395 (47.5%)	3,075 (48.3%)	17,230 (46.5%)
	Ex-smoker (1)	13,188 (21.9%)	68,751 (20.9%)	1,366 (21.5%)	8,161 (22.0%)
	Non-smoker (0)	17,792 (29.5%)	104,289 (31.7%)	1,925 (30.2%)	11,655 (31.5%)
	Missing	33,801	224,072	3,655	21,806
IMD Quintile, n (%)	1 (least deprived)	20,319 (21.6%)	130,339 (23.9%)	2,075 (20.8%)	13,374 (22.8%)
	2	20,150 (21.5%)	120,569 (22.1%)	2,088 (20.9%)	12,682 (21.6%)
	3	18,773 (20.0%)	108,790 (19.9%)	1,970 (19.7%)	12,334 (21.0%)
	4	17,881 (19.0%)	98,049 (18.0%)	1,944 (19.5%)	10,777 (18.3%)
	5 (most deprived)	16,798 (17.9%)	87,676 (16.1%)	1,916 (19.2%)	9,594 (16.3%)
	Missing	136	8,084	28	91
Charlson comorbidity score, median (IQR)		3.0 (1.0, 4.0)	2.0 (0.0, 3.0)	3.0 (1.0, 4.0)	2.0 (1.0, 4.0)
	0	14,503 (15.4%)	171,340 (31.0%)	1,468 (14.6%)	8,981 (15.3%)
	1-2	32,187 (34.2%)	199,750 (36.1%)	3,373 (33.7%)	20,945 (35.6%)
	3-4	26,384 (28.1%)	118,570 (21.4%)	2,884 (28.8%)	16,430 (27.9%)
	5-6	13,266 (14.1%)	45,164 (8.2%)	1,488 (14.8%)	7,828 (13.3%)
	>7	7,717 (8.2%)	18,683 (3.4%)	808 (8.1%)	4,668 (7.9%)
Comorbidity, n (%)	Cancer	26,070 (27.7%)	103,016 (18.6%)	2,626 (26.2%)	17,313 (29.4%)
	Cerebrovascular Disease	18,233 (19.4%)	77,420 (14.0%)	2,107 (21.0%)	12,534 (21.3%)
	COPD	16,525 (17.6%)	77,899 (14.1%)	1,722 (17.2%)	10,547 (17.9%)
	Heart Failure	14,035 (14.9%)	47,522 (8.6%)	1,724 (17.2%)	9,079 (15.4%)
	Dementia	10,338 (11.0%)	42,997 (7.8%)	893 (8.9%)	4,989 (8.5%)
	Diabetes	24,100 (25.6%)	92,909 (16.8%)	2,665 (26.6%)	12,875 (21.9%)
	HIV	6 (0.0%)	104 (0.0%)	1 (0.0%)	6 (0.0%)
	Liver Disease	1,114 (1.2%)	2,306 (0.4%)	156 (1.6%)	590 (1.0%)
	Renal Disease	30,802 (32.7%)	136,879 (24.7%)	3,464 (34.6%)	18,291 (31.1%)
	Peripheral Vascular Disease	9,697 (10.3%)	36,128 (6.5%)	1,113 (11.1%)	6,051 (10.3%)
	Autoimmnune Disease	10,620 (11.3%)	41,421 (7.5%)	1,146 (11.4%)	5,948 (10.1%)
	Deep Vein Thrombosis	1,232 (1.3%)	4,741 (0.9%)	124 (1.2%)	671 (1.1%)
	Skin Ulcer	12,553 (13.3%)	35,394 (6.4%)	1,373 (13.7%)	5,783 (9.8%)
	Coronary Heart Disease	23,858 (25.4%)	112,351 (20.3%)	2,704 (27.0%)	17,932 (30.5%)
	Hypertension	56,630 (60.2%)	304,725 (55.1%)	6,130 (61.2%)	35,063 (59.6%)

Table S4.5 *Baseline demographics and comorbidities for patients with at least three years of prior follow-up*

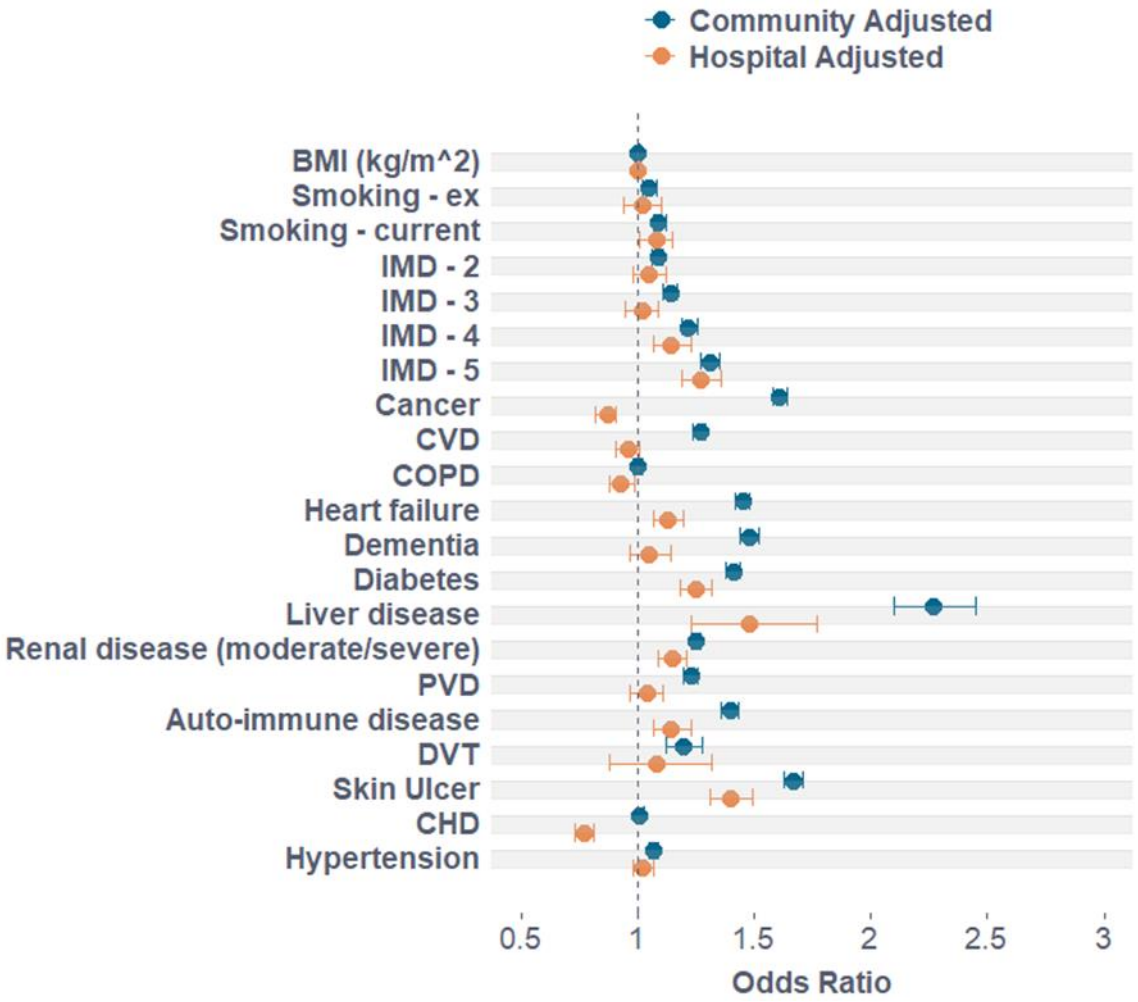


Figure S4.1 *Fully adjusted conditional logistic model results for demographic and comorbidity variables for patients with at least three years of prior follow-up*

		Community Cohort (3yr)			Hospital Cohort (3yr)		
Covariate		OR	95% CI	p-value	OR	95% CI	p-value
Charlson comorbidity score	1-2	2.03	1.99, 2.07	<0.001	0.99	0.93, 1.06	0.8
	3-4	2.97	2.90, 3.04	<0.001	1.08	1.01, 1.16	0.026
	5-6	4.06	3.95, 4.17	<0.001	1.17	1.08, 1.27	<0.001
	7+	5.76	5.58, 5.95	<0.001	1.07	0.97, 1.18	0.2

Table S4.3 *Charlson comorbidity score unadjusted odds ratios for conditional logistic regression model for patients with at least three years of prior follow-up*

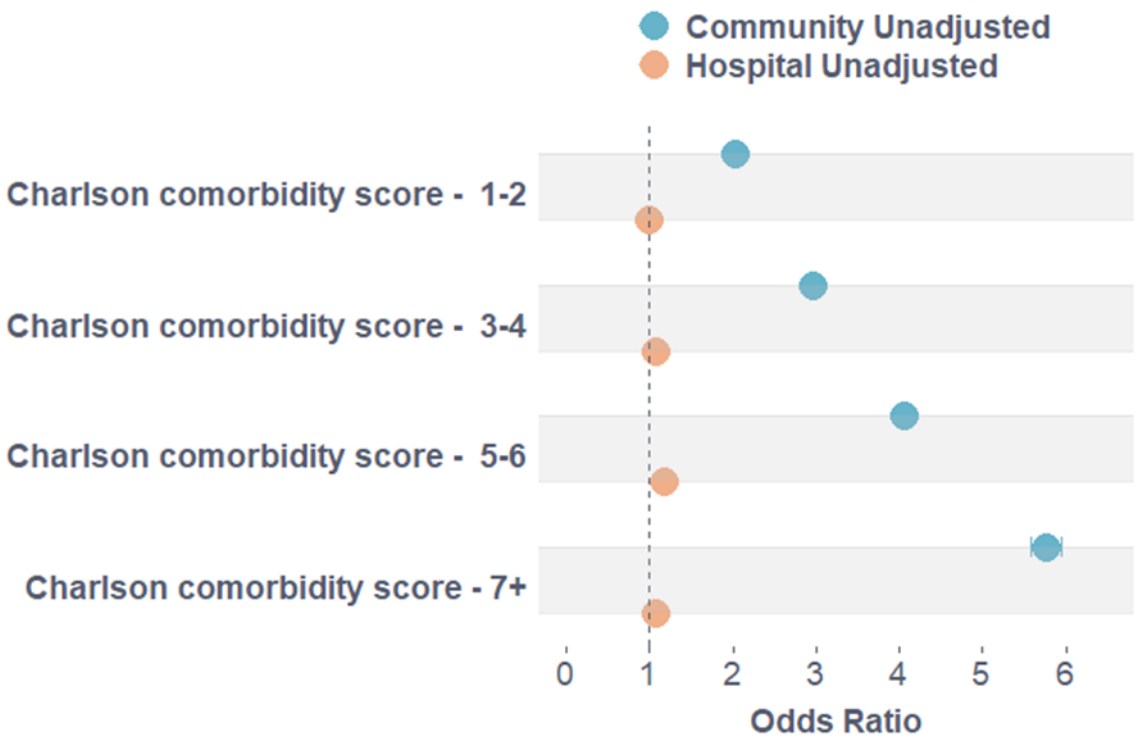


Figure S4.2 *Charlson comorbidity score unadjusted odds ratios for patients with at least three years of prior follow-up*

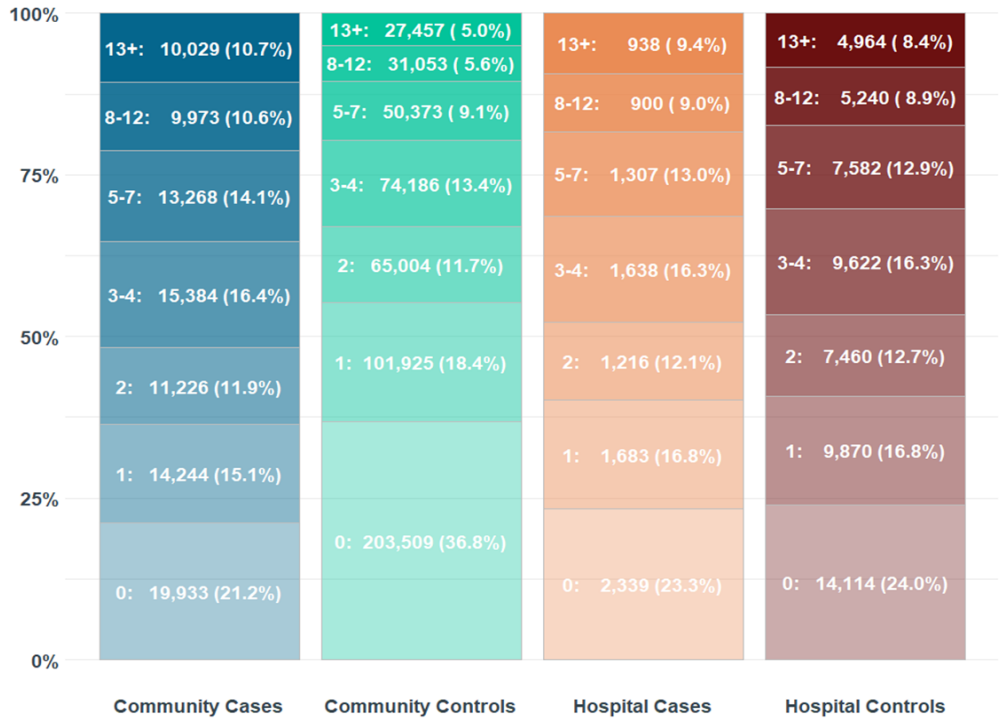


Figure S4.3 *Antibiotic use by patient group for patients with at least three years of prior follow-up*

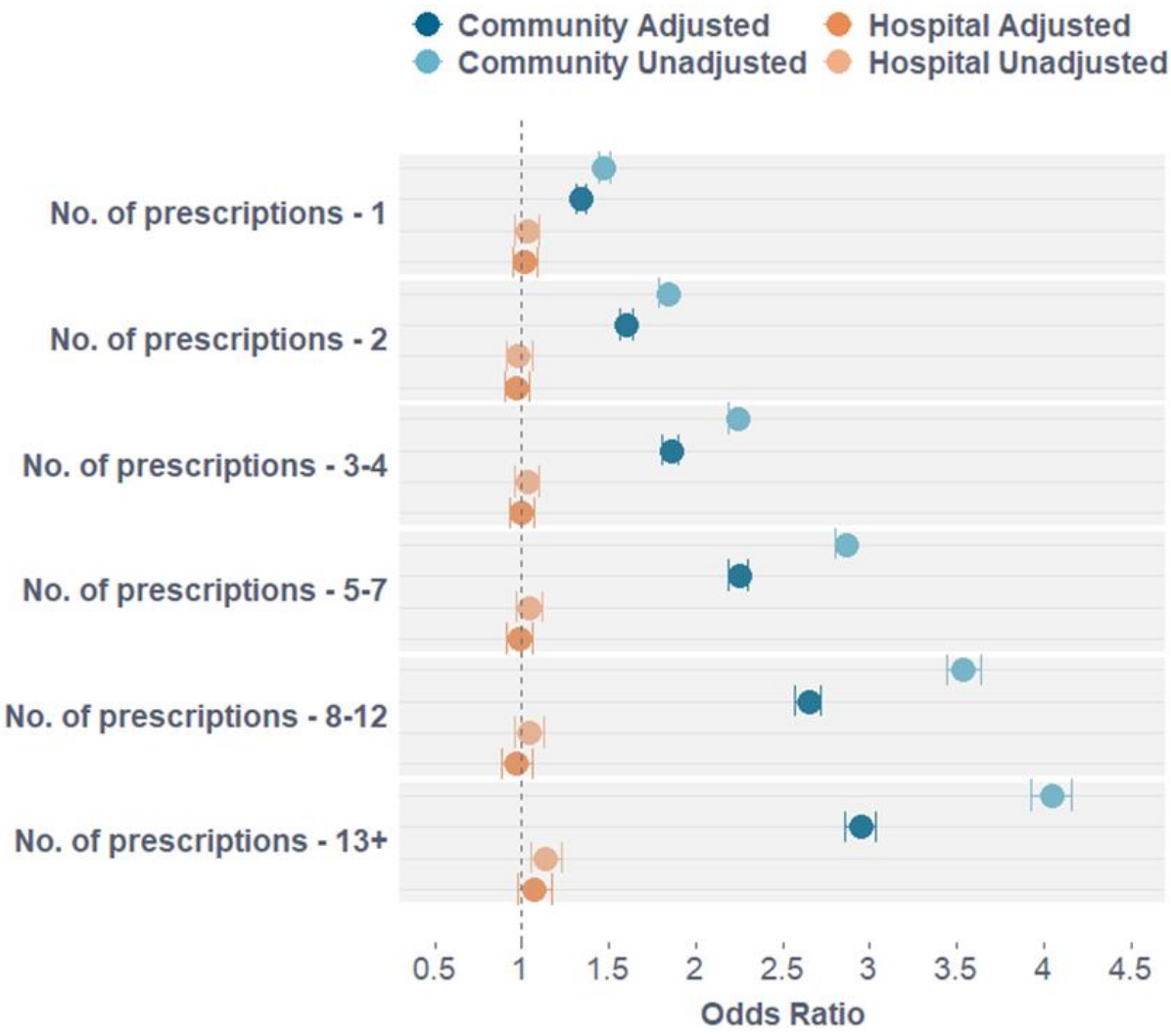


Figure S4.4 *Antibiotic use adjusted and unadjusted odds ratios for patients with at least three years of prior follow-up*

	Community Cohort (1yr)						Hospital Cohort (1yr)					
	Un-adjusted			Adjusted			Un-adjusted			Adjusted		
Covariate	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Antibiotic Prescriptions Group (ref 0) 1	1.74	1.71, 1.77	<0.001	1.57	1.54, 1.60	<0.001	1.05	0.99, 1.11	0.085	1.04	0.98, 1.10	0.2
2	2.34	2.29, 2.39	<0.001	2.02	1.97, 2.06	<0.001	1.13	1.06, 1.20	<0.001	1.10	1.03, 1.18	0.003
3-4	2.94	2.88, 3.01	<0.001	2.42	2.36, 2.47	<0.001	1.13	1.06, 1.21	<0.001	1.10	1.03, 1.18	0.005
5-6	3.49	3.38, 3.59	<0.001	2.75	2.67, 2.84	<0.001	1.18	1.08, 1.30	<0.001	1.15	1.04, 1.26	0.004
7+	3.85	3.74, 3.95	<0.001	2.98	2.89, 3.07	<0.001	1.23	1.14, 1.34	<0.001	1.19	1.09, 1.29	<0.001
BMI (kg/m^2)	1.01	1.01, 1.01	<0.001	1.00	1.00, 1.01	<0.001	1.00	1.00, 1.00	0.400	1.00	1.00, 1.01	0.4
BMI missing indicator (ref 0)	0.87	0.86, 0.89	<0.001	1.21	1.15, 1.28	<0.001	1.05	1.00, 1.11	0.046	1.18	1.01, 1.38	0.036
Smoking (ref 0, never) 1 (	1.13	1.11, 1.16	<0.001	1.05	1.02, 1.07	<0.001	1.01	0.94, 1.09	0.8	1.01	0.94, 1.08	0.9
2 (current)	1.12	1.10, 1.15	<0.001	1.09	1.07, 1.12	<0.001	1.10	1.04, 1.18	0.002	1.10	1.03, 1.17	0.005
missing	0.87	0.85, 0.89	<0.001	0.99	0.97, 1.01	0.4	1.06	1.00, 1.13	0.057	1.07	1.01, 1.14	0.021
Index of Multiple Deprivation (ref 1, least deprived) 2	1.12	1.09, 1.14	<0.001	1.09	1.06, 1.11	<0.001	1.04	0.98, 1.11	0.2	1.03	0.97, 1.10	0.3
3	1.19	1.16, 1.21	<0.001	1.13	1.11, 1.16	<0.001	1.03	0.96, 1.09	0.4	1.02	0.95, 1.08	0.6
4	1.30	1.27, 1.33	<0.001	1.22	1.19, 1.25	<0.001	1.14	1.07, 1.22	<0.001	1.13	1.06, 1.20	<0.001
5 (most deprived)	1.42	1.39, 1.46	<0.001	1.30	1.26, 1.34	<0.001	1.29	1.21, 1.38	<0.001	1.28	1.20, 1.36	<0.001
missing	0.09	0.08, 0.10	<0.001	0.08	0.07, 0.09	<0.001	1.70	1.13, 2.55	0.01	1.66	1.10, 2.50	0.015
Cancer	1.66	1.63, 1.68	<0.001	1.58	1.56, 1.61	<0.001	0.85	0.81, 0.89	<0.001	0.86	0.82, 0.90	<0.001
Cerebrovascular Disease	1.51	1.48, 1.53	<0.001	1.29	1.26, 1.31	<0.001	1.00	0.95, 1.05	>0.9	0.98	0.93, 1.03	0.4
COPD	1.28	1.26, 1.31	<0.001	1.01	0.99, 1.03	0.3	0.94	0.89, 0.99	0.025	0.92	0.87, 0.97	0.002
Heart Failure	1.88	1.85, 1.92	<0.001	1.46	1.43, 1.49	<0.001	1.13	1.07, 1.19	<0.001	1.11	1.05, 1.18	<0.001
Dementia	1.56	1.52, 1.59	<0.001	1.51	1.48, 1.55	<0.001	1.14	1.06, 1.22	<0.001	1.12	1.04, 1.20	0.002
Diabetes	1.73	1.70, 1.75	<0.001	1.43	1.41, 1.46	<0.001	1.29	1.23, 1.35	<0.001	1.25	1.19, 1.31	<0.001
HIV	0.40	0.20, 0.83	0.013	0.38	0.18, 0.79	0.008	0.86	0.11, 6.97	0.9	0.96	0.12, 7.82	>0.9
Liver Disease	2.89	2.70, 3.10	<0.001	2.30	2.15, 2.48	<0.001	1.55	1.31, 1.85	<0.001	1.46	1.23, 1.74	<0.001
Renal Disease	1.56	1.54, 1.59	<0.001	1.25	1.23, 1.27	<0.001	1.19	1.13, 1.24	<0.001	1.15	1.09, 1.20	<0.001
Peripheral Vascular Disease	1.64	1.61, 1.68	<0.001	1.23	1.20, 1.26	<0.001	1.08	1.01, 1.15	0.022	1.03	0.96, 1.10	0.4
Auto-immune Disease	1.57	1.54, 1.61	<0.001	1.41	1.38, 1.44	<0.001	1.14	1.07, 1.22	<0.001	1.13	1.06, 1.21	<0.001
Deep Vein Thrombosis	1.40	1.31, 1.49	<0.001	1.11	1.04, 1.18	0.003	0.96	0.79, 1.17	0.700	0.95	0.78, 1.15	0.6
Skin Ulcers	2.28	2.23, 2.33	<0.001	1.67	1.64, 1.71	<0.001	1.43	1.35, 1.52	<0.001	1.34	1.26, 1.42	<0.001
Coronary Heart Disease	1.33	1.31, 1.35	<0.001	1.02	1.00, 1.04	0.025	0.84	0.80, 0.88	<0.001	0.78	0.74, 0.82	<0.001
Hypertension	1.22	1.20, 1.23	<0.001	1.05	1.04, 1.07	<0.001	1.05	1.01, 1.10	0.016	1.01	0.97, 1.06	0.6

Table S4.6 *Unadjusted and adjusted odds ratios for conditional logistic regression model for patients with at least 1 year prior follow-up to index*

	Community Cohort (3yr)						Hospital Cohort (3yr)					
	Un-adjusted			Adjusted			Un-adjusted			Adjusted		
Covariate	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Antibiotic Prescriptions Group (ref 0) 1	1.47	1.44, 1.51	<0.001	1.34	1.31, 1.37	<0.001	1.03	0.96, 1.10	0.4	1.02	0.95, 1.09	0.7
2	1.84	1.79, 1.89	<0.001	1.60	1.56, 1.64	<0.001	0.98	0.91, 1.06	0.6	0.97	0.90, 1.04	0.4
3-4	2.24	2.19, 2.29	<0.001	1.86	1.81, 1.90	<0.001	1.03	0.96, 1.10	0.4	1.00	0.93, 1.07	>0.9
5-7	2.87	2.80, 2.95	<0.001	2.25	2.19, 2.30	<0.001	1.04	0.97, 1.12	0.3	0.99	0.91, 1.06	0.7
8-12	3.54	3.44, 3.64	<0.001	2.65	2.57, 2.72	<0.001	1.04	0.96, 1.13	0.4	0.97	0.89, 1.06	0.5
>13	4.05	3.93, 4.16	<0.001	2.95	2.86, 3.03	<0.001	1.14	1.05, 1.23	0.003	1.07	0.98, 1.17	0.12
BMI (kg/m^2)	1.01	1.01, 1.01	<0.001	1.00	1.00, 1.01	<0.001	1.00	1.00, 1.00	0.600	1.00	1.00, 1.01	0.3
BMI missing indicator (ref 0)	0.83	0.81, 0.84	<0.001	1.20	1.14, 1.27	<0.001	1.05	0.99, 1.10	0.081	1.20	1.02, 1.41	0.026
Smoking (ref 0, never) 1 (ex	1.14	1.11, 1.17	<0.001	1.05	1.02, 1.08	0.001	1.02	0.94, 1.10	0.7	1.02	0.94, 1.10	0.7
2 (current)	1.13	1.10, 1.15	<0.001	1.09	1.07, 1.12	<0.001	1.09	1.02, 1.16	0.013	1.08	1.01, 1.15	0.024
missing	0.84	0.82, 0.86	<0.001	0.97	0.95, 0.99	0.015	1.02	0.96, 1.09	0.5	1.03	0.97, 1.10	0.3
Index of Multiple Deprivation (ref 1, least deprived) 2	1.12	1.09, 1.14	<0.001	1.09	1.06, 1.11	<0.001	1.06	0.99, 1.13	0.08	1.05	0.98, 1.12	0.14
3	1.19	1.16, 1.22	<0.001	1.14	1.11, 1.17	<0.001	1.03	0.97, 1.10	0.4	1.02	0.95, 1.09	0.6
4	1.31	1.28, 1.34	<0.001	1.22	1.19, 1.26	<0.001	1.16	1.09, 1.24	<0.001	1.14	1.07, 1.23	<0.001
5 (most deprived)	1.43	1.39, 1.48	<0.001	1.31	1.27, 1.35	<0.001	1.29	1.20, 1.38	<0.001	1.27	1.19, 1.36	<0.001
missing	0.08	0.07, 0.09	<0.001	0.07	0.06, 0.08	<0.001	1.98	1.29, 3.03	0.002	1.92	1.25, 2.95	0.003
Cancer	1.70	1.67, 1.72	<0.001	1.61	1.58, 1.64	<0.001	0.85	0.81, 0.89	<0.001	0.87	0.82, 0.91	<0.001
Cerebrovascular Disease	1.49	1.47, 1.52	<0.001	1.27	1.24, 1.29	<0.001	0.98	0.93, 1.04	0.500	0.96	0.91, 1.01	0.2
COPD	1.31	1.29, 1.34	<0.001	1.00	0.98, 1.02	0.8	0.95	0.90, 1.00	0.059	0.93	0.88, 0.99	0.022
Heart Failure	1.91	1.87, 1.95	<0.001	1.45	1.42, 1.48	<0.001	1.14	1.08, 1.21	<0.001	1.13	1.07, 1.20	<0.001
Dementia	1.51	1.48, 1.55	<0.001	1.48	1.44, 1.52	<0.001	1.06	0.98, 1.14	0.15	1.05	0.97, 1.14	0.2
Diabetes	1.73	1.71, 1.76	<0.001	1.41	1.38, 1.44	<0.001	1.30	1.23, 1.36	<0.001	1.25	1.18, 1.32	<0.001
HIV	0.34	0.15, 0.78	0.011	0.31	0.13, 0.71	0.006	1.00	0.12, 8.31	>0.9	1.08	0.13, 9.03	>0.9
Liver Disease	2.88	2.68, 3.09	<0.001	2.27	2.10, 2.45	<0.001	1.56	1.31, 1.87	<0.001	1.48	1.23, 1.77	<0.001
Renal Disease	1.59	1.56, 1.62	<0.001	1.25	1.23, 1.27	<0.001	1.19	1.14, 1.25	<0.001	1.15	1.09, 1.21	<0.001
Peripheral Vascular Disease	1.67	1.63, 1.71	<0.001	1.23	1.20, 1.26	<0.001	1.09	1.02, 1.17	0.015	1.04	0.97, 1.11	0.3
Auto-immune Disease	1.58	1.55, 1.62	<0.001	1.4	1.36, 1.43	<0.001	1.15	1.07, 1.23	<0.001	1.14	1.07, 1.23	<0.001
Deep Vein Thrombosis	1.53	1.44, 1.64	<0.001	1.2	1.12, 1.28	<0.001	1.09	0.90, 1.33	0.400	1.08	0.88, 1.32	0.5
Skin Ulcers	2.33	2.28, 2.38	<0.001	1.67	1.63, 1.71	<0.001	1.47	1.38, 1.56	<0.001	1.40	1.31, 1.49	<0.001
Coronary Heart Disease	1.35	1.33, 1.37	<0.001	1.01	1.00, 1.03	0.12	0.84	0.80, 0.88	<0.001	0.77	0.73, 0.81	<0.001
Hypertension	1.25	1.23, 1.27	<0.001	1.07	1.05, 1.09	<0.001	1.07	1.02, 1.12	0.002	1.02	0.98, 1.07	0.3

Table S4.7 *Unadjusted and adjusted odds ratios for conditional logistic regression model for patients with at least 3 years prior follow-up to index*

	Community Cohort (1yr)			Hospital Cohort (1yr)		
	Adjusted			Adjusted		
Covariate	OR	95% CI	p-value	OR	95% CI	p-value
Antibiotic Prescriptions Group (ref 0) 1	1.83	1.80, 1.87	<0.001	1.06	1.00, 1.12	0.034
2	2.41	2.36, 2.47	<0.001	1.12	1.05, 1.20	<0.001
3-4	2.92	2.86, 2.99	<0.001	1.17	1.09, 1.24	<0.001
5-6	3.45	3.35, 3.56	<0.001	1.21	1.10, 1.33	<0.001
7+	3.59	3.49, 3.69	<0.001	1.20	1.10, 1.30	<0.001
BMI (kg/m^2)	1.00	1.00, 1.00	0.007	1.00	1.00, 1.01	0.4
BMI missing indicator (ref 0)	1.20	1.14, 1.27	<0.001	1.18	1.01, 1.37	0.036
Smoking (ref 0, never) 1	1.04	1.01, 1.07	0.002	1.01	0.93, 1.08	0.9
2 (current)	1.09	1.07, 1.12	<0.001	1.10	1.03, 1.17	0.004
missing	1.00	0.98, 1.02	0.9	1.08	1.01, 1.14	0.018
Index of Multiple Deprivation (ref 1, least deprived) 2	1.09	1.06, 1.11	<0.001	1.03	0.97, 1.10	0.3
3	1.13	1.11, 1.16	<0.001	1.02	0.95, 1.08	0.6
4	1.21	1.18, 1.25	<0.001	1.13	1.06, 1.20	<0.001
5 (most deprived)	1.29	1.26, 1.33	<0.001	1.28	1.20, 1.36	<0.001
missing	0.08	0.07, 0.09	<0.001	1.66	1.11, 2.50	0.015
Cancer	1.56	1.54, 1.58	<0.001	0.86	0.82, 0.90	<0.001
Cerebrovascular Disease	1.27	1.25, 1.30	<0.001	0.98	0.93, 1.03	0.4
COPD	0.98	0.96, 0.99	0.013	0.91	0.86, 0.96	<0.001
Heart Failure	1.44	1.41, 1.47	<0.001	1.11	1.05, 1.18	<0.001
Dementia	1.48	1.45, 1.52	<0.001	1.12	1.04, 1.20	0.002
Diabetes	1.42	1.40, 1.45	<0.001	1.24	1.18, 1.31	<0.001
HIV	0.38	0.18, 0.80	0.01	0.95	0.12, 7.75	>0.9
Liver Disease	2.27	2.11, 2.44	<0.001	1.46	1.23, 1.73	<0.001
Renal Disease	1.25	1.22, 1.27	<0.001	1.15	1.09, 1.20	<0.001
Peripheral Vascular Disease	1.21	1.19, 1.25	<0.001	1.03	0.96, 1.10	0.4
Auto-immune Disease	1.39	1.36, 1.42	<0.001	1.13	1.06, 1.21	<0.001
Deep Vein Thrombosis	1.10	1.03, 1.18	0.006	0.95	0.78, 1.15	0.6
Skin Ulcers	1.62	1.58, 1.66	<0.001	1.33	1.25, 1.41	<0.001
Coronary Heart Disease	1.01	1.00, 1.03	0.2	0.78	0.74, 0.82	<0.001
Hypertension	1.05	1.04, 1.07	<0.001	1.01	0.97, 1.06	0.6

Table S4.8 *Sensitivity analysis including prescriptions within two weeks of index date*

Results presented are from a fully adjusted conditional logistic regression model, for patients with at least one year of prior follow-up

		Hospital Cohort (1yr)					
		Un-adjusted			Adjusted		
Covariate		OR	95% CI	p-value	OR	95% CI	p-value
Antibiotic Prescriptions Group (ref 0)	1	1.13	1.06, 1.19	<0.001	1.10	1.04, 1.17	0.001
	2	1.19	1.11, 1.28	<0.001	1.15	1.07, 1.23	<0.001
	3-4	1.24	1.15, 1.33	<0.001	1.17	1.09, 1.26	<0.001
	5-6	1.34	1.22, 1.49	<0.001	1.26	1.14, 1.40	<0.001
	7+	1.46	1.33, 1.60	<0.001	1.37	1.25, 1.51	<0.001
BMI (kg/m^2)		1.00	1.00, 1.00	0.14	1.00	1.00, 1.01	0.2
BMI missing indicator (ref 0)		0.99	0.94, 1.05	0.8	1.17	0.99, 1.38	0.063
Smoking (ref 0, never)	1 (ex)	1.04	0.96, 1.13	0.3	1.02	0.95, 1.11	0.6
	2 (current)	1.08	1.01, 1.15	0.033	1.07	1.00, 1.14	0.061
	missing	1.03	0.96, 1.10	0.4	1.06	1.00, 1.14	0.06
Index of Multiple Deprivation (ref 1, least deprived)	2	1.06	0.99, 1.13	0.09	1.05	0.98, 1.12	0.2
	3	1.04	0.97, 1.11	0.2	1.03	0.96, 1.10	0.4
	4	1.12	1.05, 1.21	<0.001	1.11	1.04, 1.19	0.002
	5 (most deprived)	1.28	1.20, 1.37	<0.001	1.27	1.19, 1.36	<0.001
	missing	1.63	1.04, 2.54	0.032	1.63	1.04, 2.56	0.032
Cancer		1.00	0.95, 1.05	0.9	1.00	0.95, 1.05	0.9
Cerebrovascular Disease		0.93	0.88, 0.98	0.006	0.91	0.86, 0.96	<0.001
COPD		1.02	0.97, 1.09	0.4	0.97	0.91, 1.03	0.3
Heart Failure		1.20	1.13, 1.27	<0.001	1.13	1.06, 1.20	<0.001
Dementia		0.94	0.87, 1.01	0.09	0.95	0.88, 1.02	0.2
Diabetes		1.31	1.24, 1.38	<0.001	1.23	1.17, 1.30	<0.001
HIV		0.96	0.11, 8.66	>0.9	0.88	0.10, 8.10	>0.9
Liver Disease		1.72	1.41, 2.10	<0.001	1.64	1.34, 2.00	<0.001
Renal Disease		1.25	1.19, 1.31	<0.001	1.18	1.12, 1.24	<0.001
Peripheral Vascular Disease		1.11	1.04, 1.19	0.003	1.03	0.95, 1.11	0.5
Auto-immune Disease		1.24	1.15, 1.33	<0.001	1.22	1.14, 1.31	<0.001
Deep Vein Thrombosis		0.98	0.79, 1.21	0.8	0.94	0.76, 1.17	0.6
Skin Ulcers		1.36	1.27, 1.45	<0.001	1.24	1.16, 1.33	<0.001
Coronary Heart Disease		0.99	0.94, 1.04	0.7	0.91	0.86, 0.95	<0.001
Hypertension		1.07	1.02, 1.11	0.005	1.01	0.97, 1.06	0.6

Table S4.9 *Sensitivity analysis excluding hospital patients who were could not be matched on length of stay prior to sepsis index date*

Cohort was reduced to 10,720 cases and 42,752 controls. Results presented are from unadjusted and fully adjusted conditional logistic regression model, for hospital patients only with at least one year of prior follow-up.

		Community Cohort (1yr)			Hospital Cohort (1yr)		
		Adjusted			Adjusted		
Covariate		OR	95% CI	p-value	OR	95% CI	p-value
Antibiotic Prescriptions Group (ref 0)	1	1.58	1.55, 1.60	<0.001	1.04	0.98, 1.09	0.2
	2	2.03	1.98, 2.07	<0.001	1.11	1.03, 1.18	0.003
	3-4	2.44	2.38, 2.49	<0.001	1.11	1.03, 1.18	0.003
	5-6	2.79	2.70, 2.88	<0.001	1.15	1.04, 1.26	0.005
	7+	3.04	2.95, 3.13	<0.001	1.20	1.10, 1.31	<0.001
BMI (kg/m^2)		1.00	1.00, 1.01	<0.001	1.00	1.00, 1.01	0.3
BMI missing indicator (ref 0)		1.22	1.16, 1.29	<0.001	1.19	1.02, 1.39	0.029
Smoking (ref 0, never)	1 (ex)	1.05	1.02, 1.07	<0.001	1.01	0.93, 1.08	0.9
	2 (current)	1.09	1.07, 1.12	<0.001	1.10	1.03, 1.17	0.004
	missing	0.99	0.97, 1.01	0.4	1.08	1.01, 1.15	0.016
Index of Multiple Deprivation (ref 1, least deprived)	2	1.09	1.06, 1.11	<0.001	1.04	0.97, 1.10	0.3
	3	1.14	1.11, 1.16	<0.001	1.02	0.95, 1.08	0.6
	4	1.22	1.19, 1.25	<0.001	1.13	1.06, 1.21	<0.001
	5 (most deprived)	1.30	1.27, 1.34	<0.001	1.28	1.20, 1.37	<0.001
	missing	0.08	0.07, 0.09	<0.001	1.68	1.12, 2.52	0.013
Cancer		1.59	1.56, 1.61	<0.001	0.86	0.82, 0.90	<0.001
Cerebrovascular Disease		1.29	1.27, 1.31	<0.001	0.98	0.93, 1.03	0.3
COPD		1.01	0.99, 1.03	0.3	0.91	0.86, 0.97	0.002
Heart Failure		1.47	1.44, 1.50	<0.001	1.12	1.06, 1.18	<0.001
Dementia		1.52	1.49, 1.56	<0.001	1.12	1.04, 1.20	0.002
Diabetes		1.44	1.41, 1.46	<0.001	1.24	1.18, 1.31	<0.001
HIV		0.40	0.19, 0.83	0.014	0.96	0.12, 7.83	>0.9
Liver Disease		2.33	2.16, 2.50	<0.001	1.47	1.24, 1.75	<0.001
Renal Disease		1.26	1.24, 1.28	<0.001	1.15	1.09, 1.20	<0.001
Peripheral Vascular Disease		1.23	1.20, 1.26	<0.001	1.02	0.96, 1.10	0.5
Auto-immune Disease		1.42	1.39, 1.45	<0.001	1.14	1.07, 1.21	<0.001
Deep Vein Thrombosis		1.11	1.04, 1.19	0.002	0.95	0.78, 1.16	0.6
Skin Ulcers		1.69	1.65, 1.73	<0.001	1.33	1.25, 1.42	<0.001
Coronary Heart Disease		1.02	1.00, 1.04	0.027	0.78	0.74, 0.82	<0.001
Hypertension		1.05	1.04, 1.07	<0.001	1.01	0.97, 1.06	0.5

Table S4.10 *Sensitivity analysis excluding patients with a historic GP record of sepsis*

A small number of patients had been wrongly included. Cohort was reduced to 109,067 community-acquired sepsis cases, 635,238 community controls, 11,216 hospital-acquired sepsis cases and 65,027 hospital controls. Results are from a fully adjusted conditional logistic regression model, for patients with at least one year of prior follow-up.

GOLD		Community Cohort		Hospital Cohort	
Variable		**Cases (n = 16,466)**	**Controls (n = 94,576)**	**Cases (n = 1,627)**	**Controls (n = 9,287)**
Gender, n female (%)		8,570 (52.0%)	49,440 (52.3%)	833 (51.2%)	4,774 (51.4%)
Ethnicity, n (%)	White	6,677 (94.8%)	34,019 (94.6%)	615 (95.2%)	2,845 (95.5%)
	Black	109 (1.5%)	634 (1.8%)	8 (1.2%)	36 (1.2%)
	Asian	201 (2.9%)	1,109 (3.1%)	21 (3.3%)	82 (2.8%)
	Other	54 (0.8%)	198 (0.6%)	2 (0.3%)	17 (0.6%)
	Missing	9,425	58,616	981	6,307
Age (years), median (IQR)		81.0 (74.0, 87.0)	81.0 (74.0, 87.0)	81.0 (74.0, 87.0)	81.0 (74.0, 87.0)
	60-74	4,179 (25.4%)	23,959 (25.3%)	426 (26.2%)	2,361 (25.4%)
	75-84	6,391 (38.8%)	37,444 (39.6%)	629 (38.7%)	3,506 (37.8%)
	85-94	5,207 (31.6%)	30,001 (31.7%)	515 (31.7%)	3,033 (32.7%)
	>95	689 (4.2%)	3,172 (3.4%)	57 (3.5%)	387 (4.2%)
BMI (kg/m^2), median (IQR)		26.1 (22.7, 30.0)	26.0 (23.1, 29.3)	26.0 (22.4, 29.7)	25.9 (22.8, 29.3)
	Low BMI (<18.5), n (%)	650 (5.0%)	2,581 (3.4%)	68 (5.2%)	354 (4.6%)
	Normal BMI (18.5-24), n (%)	4,682 (36.1%)	28,280 (37.1%)	503 (38.2%)	2,911 (37.5%)
	Overweight (25-30), n (%)	4,328 (33.4%)	29,142 (38.3%)	429 (32.6%)	2,805 (36.1%)
	Obese (>30), n (%)	3,295 (25.4%)	16,166 (21.2%)	317 (24.1%)	1,690 (21.8%)
	Missing, n	3,511	18,407	310	1,527
Smoking status, n (%)	Current	2,266 (14.7%)	11,020 (12.6%)	218 (14.4%)	1,182 (13.5%)
	Ex-smoker (1)	5,550 (36.0%)	29,612 (33.8%)	560 (36.9%)	3,257 (37.1%)
	Non-smoker (0)	7,610 (49.3%)	46,861 (53.6%)	741 (48.8%)	4,329 (49.4%)
	Missing	1,040	7,083	108	519
IMD Quintile, n (%)	1 (least deprived)	3,430 (20.8%)	22,315 (23.6%)	338 (20.8%)	2,150 (23.2%)
	2	3,578 (21.7%)	21,256 (22.5%)	343 (21.1%)	2,214 (23.9%)
	3	3,572 (21.7%)	20,131 (21.3%)	359 (22.1%)	2,016 (21.7%)
	4	3,201 (19.5%)	17,222 (18.2%)	313 (19.3%)	1,690 (18.2%)
	5 (most deprived)	2,674 (16.3%)	13,586 (14.4%)	272 (16.7%)	1,211 (13.0%)
	Missing	11	66	2	6
Charlson comorbidity score, median (IQR)		2.0 (1.0, 4.0)	1.0 (0.0, 3.0)	2.0 (1.0, 4.0)	2.0 (1.0, 3.0)
	0	2,921 (17.7%)	32,395 (34.3%)	290 (17.8%)	1,893 (20.4%)
	1-2	6,292 (38.2%)	35,638 (37.7%)	602 (37.0%)	3,641 (39.2%)
	3-4	4,406 (26.8%)	18,574 (19.6%)	455 (28.0%)	2,390 (25.7%)
	5-6	1,938 (11.8%)	5,982 (6.3%)	193 (11.9%)	894 (9.6%)
	>7	909 (5.5%)	1,987 (2.1%)	87 (5.3%)	469 (5.1%)
Comorbidity, n (%)	Cancer	4,003 (24.3%)	15,194 (16.1%)	379 (23.3%)	2,553 (27.5%)
	Cerebrovascular Disease	3,192 (19.4%)	12,451 (13.2%)	314 (19.3%)	1,638 (17.6%)
	COPD	2,624 (15.9%)	12,302 (13.0%)	241 (14.8%)	1,519 (16.4%)
	Heart Failure	2,128 (12.9%)	6,700 (7.1%)	241 (14.8%)	1,015 (10.9%)
	Dementia	1,996 (12.1%)	6,765 (7.2%)	153 (9.4%)	670 (7.2%)
	Diabetes	3,899 (23.7%)	14,018 (14.8%)	377 (23.2%)	1,706 (18.4%)
	HIV	2 (0.01%)	9 (<0.01%)	0	0
	Liver Disease	164 (1.0%)	291 (0.3%)	21 (1.3%)	61 (0.7%)
	Renal Disease	4,803 (29.2%)	21,162 (22.4%)	503 (30.9%)	2,413 (26.0%)
	Peripheral Vascular Disease	1,535 (9.3%)	5,588 (5.9%)	166 (10.2%)	863 (9.3%)
	Autoimmnune Disease	1,371 (8.3%)	3,640 (3.8%)	129 (7.9%)	793 (8.5%)
	Deep Vein Thrombosis	1,070 (6.5%)	4,564 (4.8%)	110 (6.8%)	631 (6.8%)
	Skin Ulcer	2,091 (12.7%)	5,529 (5.8%)	197 (12.1%)	802 (8.6%)
	Coronary Heart Disease	3,920 (23.8%)	18,579 (19.6%)	410 (25.2%)	2,428 (26.1%)
	Hypertension	9,129 (55.4%)	49,262 (52.1%)	918 (56.4%)	5,060 (54.5%)

Table S4.11 *Baseline demographics and comorbidities for CPRD Gold patients with at least 1 year of prior follow-up*

AURUM		Community Sepsis		Hospital Sepsis	
Variable		**Cases (n = 92,603)**	**Controls (n = 546,356)**	**Cases (n = 9,678)**	**Controls (n = 55,740)**
Gender, n female (%)		47,080 (50.8%)	277,889 (50.9%)	4,824 (49.8%)	27,902 (50.1%)
Ethnicity, n (%)	White	85,696 (95.5%)	469,986 (95.1%)	8,938 (95.2%)	52,444 (95.9%)
	Black	1,272 (1.4%)	7,840 (1.6%)	173 (1.8%)	800 (1.5%)
	Asian	2,044 (2.3%)	11,398 (2.3%)	203 (2.2%)	1,046 (1.9%)
	Other	753 (0.8%)	4,897 (1.0%)	79 (0.8%)	398 (0.7%)
	Missing	2,838	52,235	285	1,052
Age (years), median (IQR)		81.0 (74.0, 87.0)	81.0 (74.0, 87.0)	81.0 (75.0, 87.0)	82.0 (75.0, 87.0)
	60-74	24,205 (26.1%)	141,693 (25.9%)	2,340 (24.2%)	12,851 (23.1%)
	75-84	35,703 (38.6%)	211,552 (38.7%)	3,933 (40.6%)	22,417 (40.2%)
	85-94	28,702 (31.0%)	170,320 (31.2%)	3,032 (31.3%)	18,025 (32.3%)
	>95	3,993 (4.3%)	22,791 (4.2%)	373 (3.9%)	2,447 (4.4%)
BMI (kg/m^2), median (IQR)		27.0 (23.2, 30.2)	26.7 (23.4, 29.4)	27.0 (23.0, 29.8)	26.9 (23.2, 29.6)
	Low BMI (<18.5), n (%)	1,736 (4.3%)	6,565 (2.9%)	172 (4.5%)	835 (3.7%)
	Normal BMI (18.5-24), n (%)	12,768 (31.5%)	75,603 (33.3%)	1,224 (31.7%)	7,373 (32.6%)
	Overweight (25-30), n (%)	15,374 (38.0%)	94,485 (41.6%)	1,521 (39.4%)	9,165 (40.6%)
	Obese (>30), n (%)	10,597 (26.2%)	50,403 (22.2%)	943 (24.4%)	5,221 (23.1%)
	Missing, n	52,128	319,300	5,818	33,146
Smoking status, n (%)	Current	29,837 (56.5%)	161,839 (56.1%)	3,113 (56.4%)	17,221 (54.1%)
	Ex-smoker	9,518 (18.0%)	49,749 (17.2%)	959 (17.4%)	5,791 (18.2%)
	Non-smoker	13,472 (25.5%)	77,101 (26.7%)	1,452 (26.3%)	8,837 (27.7%)
	Missing	39,776	257,667	4,154	23,891
IMD Quintile, n (%)	1 (least deprived)	20,071 (21.7%)	127,742 (23.8%)	2,014 (20.9%)	12,590 (22.6%)
	2	19,748 (21.4%)	117,958 (22.0%)	1,992 (20.6%)	11,821 (21.2%)
	3	18,194 (19.7%)	105,681 (19.7%)	1,866 (19.3%)	11,595 (20.8%)
	4	17,608 (19.1%)	96,937 (18.1%)	1,862 (19.3%)	10,250 (18.4%)
	5 (most deprived)	16,808 (18.2%)	88,294 (16.5%)	1,916 (19.9%)	9,378 (16.9%)
	Missing	174	9,744	28	106
Charlson comorbidity score, median (IQR)		2.0 (1.0, 4.0)	2.0 (0.0, 3.0)	3.0 (1.0, 4.0)	2.0 (1.0, 4.0)
	0	14,767 (15.9%)	169,964 (31.1%)	1,471 (15.2%)	8,532 (15.3%)
	1-2	32,047 (34.6%)	197,525 (36.2%)	3,288 (34.0%)	19,886 (35.7%)
	3-4	25,588 (27.6%)	116,051 (21.2%)	2,725 (28.2%)	15,467 (27.7%)
	5-6	12,734 (13.8%)	44,251 (8.1%)	1,422 (14.7%)	7,412 (13.3%)
	>7	7,467 (8.1%)	18,565 (3.4%)	772 (8.0%)	4,443 (8.0%)
Comorbidity, n (%)	Cancer	25,043 (27.0%)	101,109 (18.5%)	2,520 (26.0%)	16,234 (29.1%)
	Cerebrovascular Disease	18,242 (19.7%)	77,993 (14.3%)	2,070 (21.4%)	12,087 (21.7%)
	COPD	15,712 (17.0%)	75,394 (13.8%)	1,642 (17.0%)	9,894 (17.8%)
	Heart Failure	14,026 (15.1%)	48,578 (8.9%)	1,655 (17.1%)	8,932 (16.0%)
	Dementia	11,271 (12.2%)	47,775 (8.7%)	907 (9.4%)	4,760 (8.5%)
	Diabetes	23,426 (25.3%)	91,418 (16.7%)	2,560 (26.5%)	12,242 (22.0%)
	HIV	6 (<0.01%)	109 (0.02%)	1 (0.01%)	7 (0.01%)
	Liver Disease	1,100 (1.2%)	2,310 (0.4%)	150 (1.5%)	571 (1.0%)
	Renal Disease	28,942 (31.3%)	129,672 (23.7%)	3,205 (33.1%)	16,977 (30.5%)
	Peripheral Vascular Disease	9,315 (10.1%)	35,324 (6.5%)	1,054 (10.9%)	5,704 (10.2%)
	Autoimmune Disease	9,183 (9.9%)	26,656 (4.9%)	899 (9.3%)	4,925 (8.8%)
	Deep Vein Thrombosis	189 (0.2%)	693 (0.1%)	15 (0.2%)	114 (0.2%)
	Skin Ulcer	12,003 (13.0%)	34,768 (6.4%)	1,303 (13.5%)	5,531 (9.9%)
	Coronary Heart Disease	23,369 (25.2%)	111,177 (20.3%)	2,621 (27.1%)	17,233 (30.9%)
	Hypertension	54,589 (58.9%)	296,331 (54.2%)	5,814 (60.1%)	33,040 (59.3%)

Table S4.12 *Baseline demographics and comorbidities for CPRD Aurum patients for patients with at least 1 year prior follow-up*

	Community Cohort (1yr)						Hospital Cohort (1yr)					
	Un-adjusted			Adjusted			Un-adjusted			Adjusted		
Covariate	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Antibiotic Prescriptions Group (ref 0)	1.73	1.66, 1.82	<0.001	1.59	1.51, 1.66	<0.001	0.98	0.85, 1.13	0.800	0.98	0.85, 1.13	0.800
2	2.40	2.27, 2.53	<0.001	2.07	1.96, 2.19	<0.001	1.13	0.95, 1.33	0.200	1.10	0.92, 1.30	0.300
3-4	3.22	3.04, 3.40	<0.001	2.67	2.52, 2.83	<0.001	1.26	1.07, 1.49	0.006	1.22	1.03, 1.45	0.023
5-6	3.98	3.68, 4.31	<0.001	3.18	2.93, 3.45	<0.001	1.08	0.83, 1.40	0.600	1.04	0.79, 1.36	0.800
7+	4.43	4.12, 4.75	<0.001	3.36	3.12, 3.63	<0.001	1.29	1.04, 1.61	0.023	1.24	0.99, 1.56	0.063
BMI (kg/m^2)	1.00	1.00, 1.00	0.300	1.00	1.00, 1.01	0.068	1.00	0.99, 1.00	0.200	1.00	0.99, 1.01	0.600
BMI missing indicator (ref 0)	1.15	1.09, 1.20	<0.001	1.55	1.39, 1.73	<0.001	1.21	1.04, 1.40	0.011	1.34	0.97, 1.86	0.075
Smoking (ref 0, never)	1.19	1.14, 1.23	<0.001	1.07	1.03, 1.12	0.001	1.00	0.89, 1.14	>0.9	0.99	0.88, 1.13	>0.9
2 (current)	1.31	1.24, 1.38	<0.001	1.27	1.20, 1.35	<0.001	1.08	0.91, 1.28	0.400	1.08	0.91, 1.28	0.400
missing	0.86	0.79, 0.93	<0.001	0.93	0.86, 1.02	0.140	1.22	0.95, 1.58	0.120	1.19	0.91, 1.55	0.200
Index of Multiple Deprivation (ref 1, least dep	1.16	1.10, 1.23	<0.001	1.14	1.07, 1.21	<0.001	0.99	0.84, 1.16	>0.9	0.96	0.82, 1.14	0.700
3	1.27	1.20, 1.35	<0.001	1.20	1.13, 1.28	<0.001	1.14	0.97, 1.34	0.100	1.10	0.94, 1.30	0.200
4	1.38	1.30, 1.47	<0.001	1.29	1.20, 1.37	<0.001	1.19	1.00, 1.41	0.045	1.12	0.95, 1.33	0.200
5 (most deprived)	1.52	1.42, 1.63	<0.001	1.36	1.27, 1.46	<0.001	1.43	1.20, 1.70	<0.001	1.37	1.14, 1.63	<0.001
missing												
Cancer	1.69	1.62, 1.76	<0.001	1.42	1.35, 1.49	<0.001	0.80	0.70, 0.91	<0.001	0.83	0.72, 0.95	0.008
Cerebrovascular Disease	1.59	1.52, 1.66	<0.001	1.35	1.29, 1.42	<0.001	1.12	0.98, 1.28	0.100	1.07	0.93, 1.23	0.300
COPD	1.28	1.22, 1.34	<0.001	1.00	0.95, 1.05	>0.9	0.89	0.76, 1.03	0.120	0.87	0.75, 1.02	0.079
Heart Failure	1.97	1.87, 2.08	<0.001	1.53	1.44, 1.62	<0.001	1.45	1.24, 1.69	<0.001	1.40	1.19, 1.64	<0.001
Dementia	1.84	1.74, 1.95	<0.001	1.72	1.62, 1.82	<0.001	1.35	1.12, 1.63	0.002	1.29	1.07, 1.56	0.009
Diabetes	1.81	1.74, 1.89	<0.001	1.58	1.51, 1.65	<0.001	1.35	1.19, 1.54	<0.001	1.26	1.09, 1.44	0.001
HIV	1.31	0.28, 6.07	0.700	0.66	0.14, 3.21	0.600				—	—	
Liver Disease	3.34	2.75, 4.05	<0.001	2.48	2.02, 3.06	<0.001	1.92	1.16, 3.18	0.011	1.76	1.06, 2.94	0.030
Renal Disease	1.52	1.46, 1.58	<0.001	1.22	1.17, 1.28	<0.001	1.35	1.19, 1.53	<0.001	1.25	1.09, 1.42	<0.001
Peripheral Vascular Disease	1.65	1.56, 1.76	<0.001	1.22	1.14, 1.30	<0.001	1.12	0.94, 1.34	0.200	1.00	0.83, 1.20	>0.9
Auto-immune Disease	2.32	2.17, 2.47	<0.001	1.74	1.61, 1.87	<0.001	0.91	0.75, 1.11	0.400	1.08	0.87, 1.35	0.500
Deep Vein Thrombosis	1.37	1.27, 1.46	<0.001	1.07	1.00, 1.16	0.057	1.01	0.82, 1.24	>0.9	0.98	0.79, 1.21	0.800
Skin Ulcers	2.40	2.27, 2.53	<0.001	1.73	1.64, 1.84	<0.001	1.48	1.25, 1.74	<0.001	1.35	1.14, 1.60	<0.001
Coronary Heart Disease	1.29	1.24, 1.34	<0.001	1.01	0.97, 1.05	0.700	0.96	0.85, 1.08	0.500	0.85	0.75, 0.97	0.018
Hypertension	1.15	1.12, 1.19	<0.001	1.03	0.99, 1.07	0.095	1.10	0.98, 1.22	0.100	1.05	0.93, 1.17	0.400

Table S4.13 *Conditional logistic regression results for Gold patients with at least 1 year prior follow-up*

	Community Cohort (1yr)						Hospital Cohort (1yr)					
	Un-adjusted			Adjusted			Un-adjusted			Adjusted		
Covariate	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Antibiotic Prescriptions Group (ref 0)	1.74	1.71, 1.77	<0.001	1.57	1.54, 1.60	<0.001	1.06	1.00, 1.12	0.049	1.05	0.99, 1.11	0.100
2	2.33	2.28, 2.39	<0.001	2.01	1.96, 2.06	<0.001	1.13	1.05, 1.21	0.001	1.11	1.03, 1.19	0.005
3-4	2.90	2.83, 2.97	<0.001	2.38	2.32, 2.44	<0.001	1.11	1.04, 1.19	0.003	1.08	1.01, 1.16	0.031
5-6	3.40	3.30, 3.52	<0.001	2.68	2.59, 2.78	<0.001	1.20	1.09, 1.32	0.000	1.17	1.06, 1.29	0.002
7+	3.75	3.64, 3.87	<0.001	2.91	2.82, 3.00	<0.001	1.22	1.12, 1.34	0.000	1.19	1.08, 1.30	<0.001
BMI (kg/m^2)	1.01	1.01, 1.01	<0.001	1.00	1.00, 1.01	0.004	1.00	1.00, 1.00	0.659	1.00	1.00, 1.01	0.70
BMI missing indicator (ref 0)	0.83	0.81, 0.85	<0.001	1.16	1.09, 1.23	<0.001	1.03	0.98, 1.09	0.217	1.12	0.94, 1.34	0.20
Smoking (ref 0, never)	1.10	1.07, 1.14	<0.001	1.04	1.01, 1.07	0.015	1.01	0.92, 1.11	0.807	1.01	0.92, 1.11	0.80
2 (current)	1.09	1.06, 1.12	<0.001	1.07	1.04, 1.09	<0.001	1.11	1.03, 1.18	0.005	1.10	1.02, 1.18	0.01
missing	0.85	0.83, 0.87	<0.001	0.97	0.95, 1.00	0.029	1.06	0.99, 1.13	0.103	1.07	1.00, 1.14	0.052
Index of Multiple Deprivation (ref 1, least depr	1.11	1.08, 1.13	<0.001	1.08	1.05, 1.10	<0.001	1.05	0.98, 1.12	0.150	1.05	0.98, 1.12	0.20
3	1.07	1.04, 1.10	<0.001	1.02	0.99, 1.05	0.12	1.01	0.95, 1.08	0.700	1.01	0.94, 1.08	>0.9
4	1.29	1.25, 1.32	<0.001	1.20	1.17, 1.24	<0.001	1.13	1.06, 1.21	<0.001	1.12	1.05, 1.20	0.001
5 (most deprived)	1.42	1.38, 1.46	<0.001	1.29	1.26, 1.33	<0.001	1.27	1.19, 1.36	<0.001	1.26	1.17, 1.35	<0.001
missing												
Cancer	1.65	1.63, 1.68	<0.001	1.38	1.36, 1.41	<0.001	0.86	0.82, 0.90	0.000	0.82	0.78, 0.87	<0.001
Cerebrovascular Disease	1.49	1.46, 1.52	<0.001	1.28	1.25, 1.30	<0.001	0.98	0.93, 1.03	0.452	0.97	0.92, 1.02	0.20
COPD	1.29	1.26, 1.31	<0.001	1.02	1.00, 1.04	0.025	0.95	0.90, 1.00	0.073	0.93	0.87, 0.98	0.01
Heart Failure	1.87	1.83, 1.91	<0.001	1.45	1.41, 1.48	<0.001	1.09	1.03, 1.15	0.005	1.08	1.02, 1.15	0.013
Dementia	1.52	1.48, 1.55	<0.001	1.48	1.44, 1.51	<0.001	1.11	1.03, 1.20	0.008	1.09	1.01, 1.18	0.024
Diabetes	1.71	1.68, 1.74	<0.001	1.41	1.38, 1.44	<0.001	1.28	1.22, 1.35	0.000	1.24	1.18, 1.31	<0.001
HIV	0.33	0.14, 0.74	0.008	0.20	0.09, 0.47	<0.001	0.86	0.11, 6.97	0.885	0.80	0.10, 6.58	0.80
Liver Disease	2.84	2.64, 3.05	<0.001	2.24	2.07, 2.42	<0.001	1.51	1.26, 1.82	0.000	1.42	1.18, 1.70	<0.001
Renal Disease	1.57	1.55, 1.60	<0.001	1.26	1.24, 1.28	<0.001	1.16	1.11, 1.22	0.000	1.13	1.07, 1.19	<0.001
Peripheral Vascular Disease	1.64	1.60, 1.68	<0.001	1.23	1.20, 1.26	<0.001	1.07	1.00, 1.15	0.051	1.03	0.96, 1.11	0.40
Auto-immune Disease	2.17	2.12, 2.23	<0.001	1.64	1.59, 1.69	<0.001	1.06	0.99, 1.15	0.105	1.20	1.11, 1.31	<0.001
Deep Vein Thrombosis	1.63	1.38, 1.91	<0.001	1.27	1.07, 1.50	0.003	0.75	0.43, 1.28	0.290	0.73	0.42, 1.26	0.30
Skin Ulcers	2.26	2.21, 2.31	<0.001	1.68	1.64, 1.72	<0.001	1.42	1.33, 1.52	0.000	1.34	1.26, 1.44	<0.001
Coronary Heart Disease	1.34	1.31, 1.36	<0.001	1.03	1.01, 1.05	0.003	0.83	0.79, 0.87	0.000	0.77	0.73, 0.81	<0.001
Hypertension	1.23	1.21, 1.25	<0.001	1.06	1.04, 1.08	<0.001	1.05	1.00, 1.09	0.054	1.01	0.96, 1.05	0.80

Table S4.14 *Conditional logistic regression results for Aurum patients with at least 1 year prior follow-up*

Chapter 5 - Exploring the antimicrobial burden of sepsis patients admitted to intensive care

5.1 Abstract

Globally, it is estimated there are around 49 million cases of sepsis each year, resulting in around 11 million deaths [1]. Antimicrobials are vital in treating sepsis, however, their use is under threat due to resistance. More optimal use of antimicrobials is needed, in order to reduce overall consumption without impacting patient outcomes. The aims of this paper are to explore the antibiotic burden of sepsis patients in an ICU setting and to look at the association between use of antimicrobials and mortality.

Cohort study using the MIMIC-III database. Patients who met the Sepsis-3 criteria on admission to ICU were identified and data about their demographics and antimicrobial use was extracted. Variables were created for exposure to antimicrobials. Survival analysis was carried out using Kaplan-Meier curves and Cox regression analysis.

8,639 patients (of 23,620 admissions, 36.6%) met the sepsis-3 criteria, who had a median age of 68 years (IQR 55–80), a median SOFA score of 5 (3-7) and a median Elixhauser comorbidity index of 4 (0-9). Subgroups of the cohort based on ICD-9 codes (Angus criteria, Martin criteria and explicit sepsis ICD-9 codes) had higher levels of comorbidity and organ dysfunction. Antibiotics accounted for 94% of antimicrobials prescribed during the admissions, with vancomycin the most frequently used. Patients received a median of 3 courses (2-5) of antimicrobials and exposed to antimicrobials for a median of 5 days (3-9). ICU mortality was 14% and 30-day mortality was 22% for the full cohort with the sub-cohorts having higher mortality. Older patients had a slightly higher risk of mortality (adjusted HR 1.02, 95% CI 1.02-1.02), males had a lower risk than females (adjusted HR 0.92, 95% CI 0.84-1.01). Increased SOFA score was associated with higher mortality (adjusted HR 1.33, 95% CI 1.30-1.37) as was an increased number of different antimicrobials prescribed (adjusted HR 1.2, 95% CI 1.17-1.22). Patients who were exposed to antimicrobials for more days in the follow-up period had a lower risk of mortality (adjusted HR 0.92, 95%CI 0.90-0.93).

5.2 Introduction

Sepsis is “life-threatening organ dysfunction caused by a dysregulated host response to infection” [2]. It is estimated that in 2017 there were 48.9 million cases around the world, leading

to over 11 million deaths [1]. As well as mortality, patients who survive sepsis often experience long-term complications, placing a large burden on health services [34].

Resistance to antimicrobials is increasing around the world, meaning more people are at risk of dying from infections and developing conditions such as sepsis. There are pressures across both community and hospital care to reduce the consumption of antibiotics in order to slow down emerging resistance [5]. In patients with sepsis, however, prompt administration of antibiotics is recommended as soon as it is suspected [6]. A global prevalence audit reported that of 10,069 ICU patients, 5,975 (59.3%) received antimicrobials and of the 2,973 (29.5%) of those patients with sepsis, 100% were prescribed at least one antimicrobial [7]. Treating infections in critically ill patients is complex; delays in starting antibiotics has been shown to increase mortality rates in patients with severe sepsis or septic shock, however inappropriate empirical therapy has also been shown to have an adverse impact. Therefore, in patients with less severe sepsis waiting to begin treatment until infection is confirmed may be beneficial to patients. Other studies have shown that shorter courses of antibiotics have a positive effect on mortality rates.

For complex conditions such as sepsis the increasing availability of electronic health record data means that large cohorts can be studied at a greater level of detail.

Aims:

This study aimed to explore the antibiotic burden of sepsis patients in intensive care units (ICU) using electronic health record data and to look at the association between use of antibiotics and mortality.

5.3 Methods

5.3.1 Data Source

The data for this study comes from the Medical Information Mart for Intensive Care III (MIMIC-III, version 1.4) database, a large, freely-available dataset consisting of anonymised health records of over 40,000 patients treated in the critical care units of the Beth Israel Deaconess Medical Centre (BIDMC) in Boston, USA. The dataset covers all ICU stays between 2001 and 2012 and consists of 26 tables containing a range of information including clinical measurements, laboratory test results and drug prescriptions. The MIMIC database provides data captured by two different clinical information systems; CareVue and Metavision used at different time periods. Only the Metavision system captured all drug prescriptions and drug administrations data, between 2008 and 2012, so this study only used Metavision data. The access and use of the MIMIC-III database was approved following completion of an online

training course [8,9]. A local version of the database was built using PostgreSQL and queried using SQL.

5.3.2 Patients

Adults admitted to ICU with sepsis between 2008 and 2012 were identified using multiple criteria described by Johnson et al [10]. Patients were included if they met the Sepsis-3 criteria [2] of suspected infection (blood cultures taken and antibiotics given) and associated organ dysfunction (Sequential Organ Failure Assessment[11] (SOFA) score $\geq$ 2). The cohort was divided into subgroups based around ICD-9 codes, patients with an explicit ICD-9 code for severe sepsis or septic shock, patients who met the Angus[12] criteria and those who met the Martin[13] criteria. Both the Angus and Martin criteria are comprehensive groups of procedural and diagnostic ICD-9 codes indicative of sepsis. Admissions where the patient had a prior admission for sepsis were excluded in order to capture incident episodes of sepsis. Additionally, admissions of patients from the cardiothoracic surgical service and patients suspected of infection more than 24 hours after ICU admission were excluded (see Figure 1). Patients aged 89 or over at the time of admission had their ages obscured in the database, for privacy reasons, so for this analysis age for these patients was imputed as the median (91.4)[9]. The index date for each patient was the date of admission to ICU.

5.3.3 Variables

Data was extracted for the eligible patients using the unique patient ID, hospital stay ID and ICU stay ID for the sepsis admission. Variables included in analysis were age, gender (male/ female), ethnicity (white/ black/ Hispanic/ other), admission type (elective/ emergency/ urgent), Elixhauser comorbidity score (grouped as <0, 0, 1-5, 6-13 and >14) and Sequential Organ Failure Assessment (SOFA) score.

Data around antimicrobial use was taken from the prescriptions and input events tables and extracted using the unique ICU stay ID. The input events data is a record of each individual IV administration of an antimicrobial and is available for the patient's ICU admission. These were identified using item IDs listed in the items table, labelled as antimicrobials. The prescriptions data is available for the full period of the hospital admission and includes drugs administered by all routes, although it does not report on how frequently doses were administered. All prescriptions of antimicrobials were extracted for the cohort patients by filtering the table by type of drug. Entries in the prescriptions table were not labelled with item IDs but with the name of the drug, with variations in how the same drugs had been spelled

and formatted. The names of the drugs were cleaned and formatted to match the drug names in the items table and IV input table. Prescriptions recorded as the drug brand name were changed to their respective generic names.

For entries in both the IV events and prescriptions tables duplicate entries, those with no start or end date, those missing the drug name, those whose start date did not fall between the hospital or ICU start and end dates, or whose start date was recorded as being after the patients recorded date of death were all excluded. Prescriptions for the same drug, route and dose were combined if they overlapped or followed on directly from one another. Prescriptions that ended after the 30-day follow-up date were truncated at the end of follow-up date. Assumptions were made that patients received doses of the antimicrobial on each day that the prescription was valid for and that if the patient was discharged from ICU to another hospital ward the prescription remained valid until its end date.

5.3.4 Statistical methods

Baseline demographics and clinical characteristics were summarised for the full cohort and sub-cohorts. Continuous variables were reported as mean and standard error or median and interquartile range depending on normality, categorical variables as number and percent. Some continuous variables were grouped to show the distribution of the data but included in the model as continuous.

Overall antimicrobial use was summarised for the cohort, from the beginning of ICU admission to hospital discharge or the end of the 30-day follow up period. The number of different antimicrobial courses and the number of days in the follow up period where the patient had an active drug prescription were calculated. Additionally, the cumulative number of exposure days was calculated, where if patients had multiple prescriptions for different antimicrobials on a single day they were counted multiple times. For example if a patient received 2 different antimicrobials over 4 days then their cumulative exposure days was 8 [14,15]. For antimicrobials delivered through IV the number of administrations was calculated for each antimicrobial for the ICU stay. Exposure was compared between patient characteristics including age, Elixhauser comorbidity index and SOFA score in the full cohort only.

The primary outcome was 30-day all-cause mortality, with secondary outcomes of ICU and hospital length of stay. ICU, hospital, 30-day, 90-day and 1-year mortality rates were calculated for the full cohort and sub-groups, reported as the number of deaths and %. ICU

and hospital length of stay (days) was calculated for the full cohort and subgroups, and reported as the median and IQR and grouped.

Kaplan-Meier curves were produced for the 30-day mortality outcome in the full cohort, stratifying by the patient sub-groups and patient characteristics including age, gender, ethnicity, admission type, Elixhauser comorbidity index and SOFA score.

Cox proportional hazards regression was used for modelling the 30-day all-cause mortality outcome in the full cohort only. Unadjusted hazard ratios were calculated for each variable followed by a fully adjusted multivariable model. Age, gender, ethnicity, admission type, baseline SOFA score, baseline Elixhauser comorbidity index, number of antimicrobials and number of antimicrobial exposure days were included in the model. The proportional hazards assumption was checked visually and tested statistically. Variables that violated the assumption (SOFA score and Elixhauser comorbidity index) were included in the model with an interaction with a continuous transformation of time ($\sqrt{time}$), to account for the fact that the effects of these two variables on the outcome is not proportional over the follow-up period.

As patients were given antimicrobials during the follow-up period the antibiotic exposure variables (number of antimicrobials prescribed and number of antimicrobial exposure days) changed during the follow up period. A standard Cox model only includes variables measured at baseline (for example age, gender, ethnicity, SOFA and comorbidity index here) and cannot include any information captured after the baseline time point. However, as our interest was in the effect of antibiotic exposure and this did change during follow-up these variables needed to be handled differently. An additional consideration was the implication of immortal time bias, whereby patients who die during follow-up will inherently be unable to receive antibiotics and therefore have lower exposure than patients who survived the full follow-up period and therefore able to receive more antimicrobials. The exposure variables, therefore, were included as time-varying covariates in the model[16]. At the start of each new prescription the number of exposure days and drug prescriptions were updated up until that time point for each patient. Each patient therefore had multiple entries in the dataset, including the increasing exposure to antimicrobials over the 30-days. At each time point where the event occurred the model compares were made between individuals with different levels of antimicrobial exposure at that time point.

Hazard ratios with 95% confidence intervals and p-values were reported from the model. Analysis was conducted using R, version 3.5.1, the Cox proportional hazards model was fitted using the *survival* package.

5.4 Results

Of the 23,620 admissions in the MetaVision database, 8,639 (36.6%) met the Sepsis-3 inclusion criteria (see Figure 1). Of the 8,369 patients who met the Sepsis-3 criteria 3,880 only met those criteria and 4,759 also met one of the additional ICD-9 criteria. 4,504 patients met the Angus criteria (52.1%), 2,474 met the Martin criteria (28.6%), with only 1,575 of the patients having an explicit ICD-9 code for sepsis or septic shock (18.8%). The overlap of the groups is shown below. Only 1,565 patients met all three additional criteria.

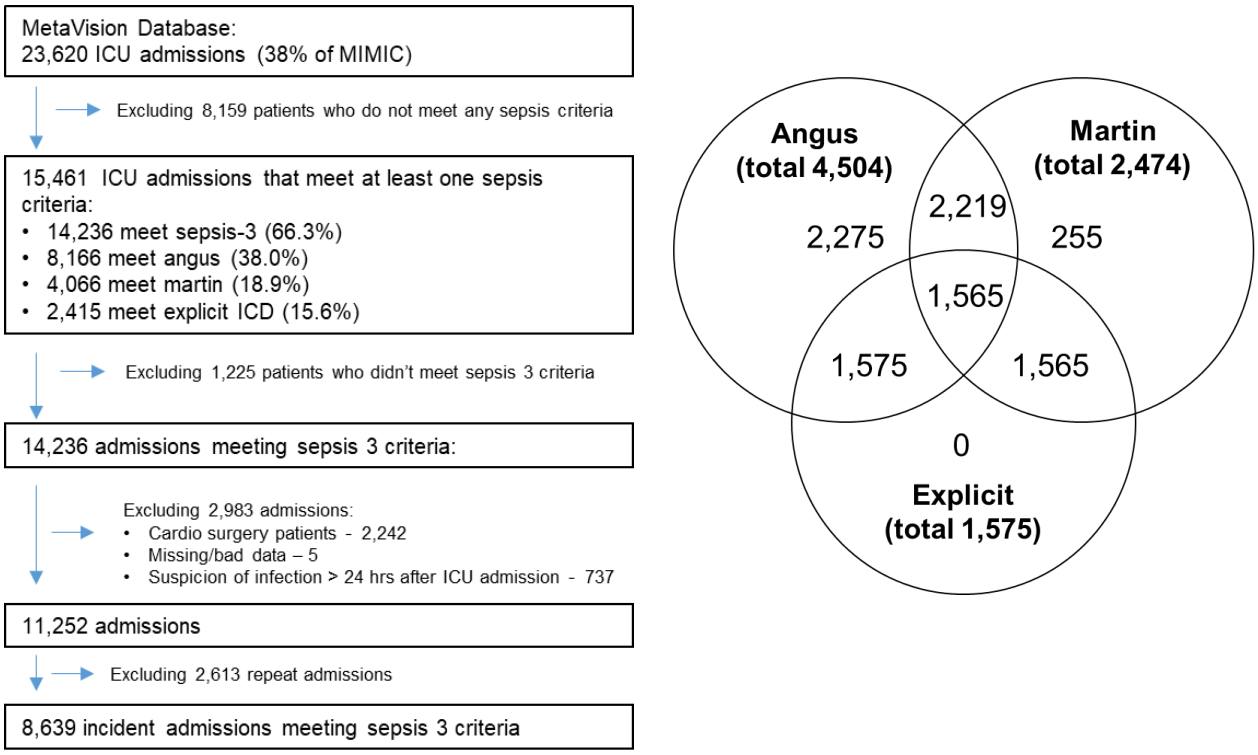


Figure 5.1 *Study patient inclusion/exclusion criteria and overlap between groups.*

Table 1 shows the baseline characteristics of the full cohort and sub-groups. 56% of the cohort were male and 74% were white, with a median age of 67.7 years (IQR 55.1 – 79.9). The patients had a median SOFA score of 5 (IQR 3–7) and a median Elixhauser comorbidity index of 4 (IQR 0–9). 75% of the patients had been in the hospital for less than 48 hours prior to admission to ICU. For the patient subgroups the median age, SOFA score and Elixhauser index increased as the subgroup size decreased, patients with an explicit code for sepsis or septic shock were older, had higher comorbidities and a higher SOFA score. 96% of patients in the explicit subgroup were emergency admissions to the hospital, compared with 93% in the overall cohort.

	All Patients	Angus	Martin	Explicit
No. of ICU admissions	8,639	4504 (52%)	2474 (29%)	1575 (18%)
Gender				
Female	3834 (44%)	2094 (46%)	1093 (44%)	703 (45%)
Male	4805 (56%)	2410 (54%)	1381 (56%)	872 (55%)
Ethnicity				
White	6351 (74%)	3311 (74%)	1832 (74%)	1169 (74%)
Black	845 (9.8%)	455 (10%)	237 (9.6%)	147 (9.3%)
Hispanic	305 (3.5%)	146 (3.2%)	83 (3.4%)	46 (2.9%)
Other	1138 (13%)	592 (13%)	322 (13%)	213 (14%)
Age (years)				
Median	67.7 (55.1, 79.9)	69.2 (56.2, 80.8)	68.7 (56.3, 80.6)	69.1 (57.4, 81.2)
17-25	174 (2.0%)	62 (1.4%)	30 (1.2%)	12 (0.8%)
26-35	304 (3.5%)	124 (2.8%)	63 (2.5%)	38 (2.4%)
36-45	529 (6.1%)	269 (6.0%)	154 (6.2%)	88 (5.6%)
46-55	1138 (13%)	579 (13%)	313 (13%)	195 (12%)
56-65	1658 (19%)	820 (18%)	472 (19%)	296 (19%)
66-75	1774 (21%)	918 (20%)	505 (20%)	320 (20%)
76-85	1855 (21%)	1050 (23%)	576 (23%)	384 (24%)
>86	1207 (14%)	682 (15%)	361 (15%)	242 (15%)
SOFA score				
Median	5 (3, 7)	5 (4, 8)	6 (4, 9)	7 (5, 10)
0-1	0 (0%)	0 (0%)	0 (0%)	0 (0%)
2-3	2744 (32%)	1044 (23%)	465 (19%)	192 (12%)
4-5	2485 (29%)	1220 (27%)	573 (23%)	301 (19%)
6-7	1517 (18%)	867 (19%)	483 (20%)	312 (20%)
8-9	856 (9.9%)	573 (13%)	362 (15%)	268 (17%)
10-11	527 (6.1%)	395 (8.8%)	267 (11%)	213 (14%)
12-13	256 (3.0%)	198 (4.4%)	152 (6.1%)	133 (8.4%)
>13	254 (2.9%)	207 (4.6%)	172 (6.9%)	157 (10.0%)
Elixhauser comorbidity index				
Median	4 (0, 9)	6 (0, 10)	6 (1, 11)	7 (2, 12)
< 0	2047 (24%)	891 (20%)	453 (18%)	248 (16%)
0	1116 (13%)	311 (6.9%)	145 (5.9%)	68 (4.3%)
1-5	1903 (22%)	1031 (23%)	541 (22%)	346 (22%)
6-13	2727 (32%)	1666 (37%)	955 (39%)	637 (40%)
> 14	846 (9.8%)	605 (13%)	380 (15%)	276 (18%)
Admission Type				
Elective	487 (5.6%)	135 (3.0%)	50 (2.0%)	39 (2.5%)
Emergency	8042 (93%)	4307 (96%)	2382 (96%)	1510 (96%)
Urgent	110 (1.3%)	62 (1.4%)	42 (1.7%)	26 (1.7%)

Table 5.1 *Baseline characteristics of sepsis patients*

There were 31,432 prescriptions for antimicrobials associated with patients in the sepsis cohort in the period from their admission to ICU to hospital discharge. 169 patients (2.0%) did not have any prescriptions recorded for after ICU admission. Antibiotics accounted for 94% of the antimicrobial prescriptions (29,662), followed by antifungal (1,164, 3.7%) and antiviral drugs (606, 1.9%). The antimicrobials were most frequently administered via IV (23,899, 76%), with 23% (7,076) administered enterally.

The most commonly prescribed antibiotics were β-lactams (34%), followed by glycopeptides (23%) and quinolones (16%). Figure 2a shows the prescriptions by type, whilst Figure 2b shows the top 10 individual most frequently prescribed antimicrobials.

Vancomycin was the most commonly prescribed antibiotic, accounting for 23% (7,141) of all prescriptions, followed by ciprofloxacin (2,977, 9.5%), metronidazole (2,846, 9.1%), piperacillin/tazobactam (2,600, 8.3%) and levofloxacin (1,998, 6.4%).Of the 23,899 prescriptions for IV antimicrobials, administration data was available for 19,644 (82.2%) of these. The median duration of prescriptions was 3 (IQR 2-6) days, and for the IV administered antimicrobials the median number of administrations for each course was 3 (IQR 2-7).

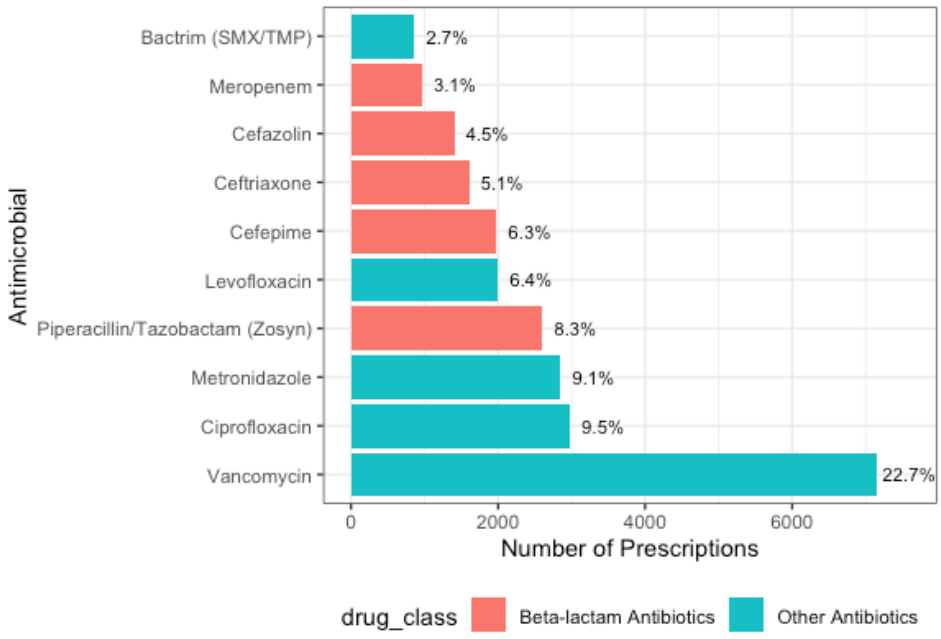


Figure 5.2 *Ten most frequently used antimicrobials*

In terms of individual patient use of antimicrobials the median number of different antimicrobials prescribed was 3 (IQR 2-5) in the overall cohort. The maximum number of prescriptions for a single patient in the follow-up period was 23. The median number for the subgroups of patients who meet the Angus, Martin and explicit code criteria was 4 (IQR 3-6), 4 (IQR 3-6) and 5 (IQR 3-7), respectively.

The median number of days in the follow-up period where patients were exposed to antimicrobials was 5 (IQR 3-9) in the overall cohort, 7 for the patients who met the Angus criteria (IQR 4-12) and 8 for patients in the Martin criteria and explicit code subgroups (IQRs 5-13 and 4-13, respectively). In terms of cumulative antimicrobial exposure the median

number of days was 10 (IQR 5-20) for the whole cohort, 15 (IQR 8-27) for patients in the Angus criteria subgroup, 17 (10-30) for patients in the Martin subgroup criteria and 18 (10-32) for patients in the explicit code subgroup.

Figure 3 shows the distribution of the number of courses and total exposure days stratified by age, SOFA score and Elixhauser comorbidity index. When looking at the antimicrobial usage in the different age groups the median number of courses prescribed is 3 for all patients, although the IQR is narrower in the >86 years patient group (2-4) vs the 17-25 years group (2-5). The median total exposure days is slightly higher in the 17-25 years patients (6, IQR 3-11) compared with the >86 years group (5, IQR 3-8). There is a larger difference in the cumulative exposure days (not shown, see supplementary Table 1) where the youngest patients (12, IQR 5-22) have been exposed on more days than older patients (9, IQR 5-16).

Patients with a higher SOFA score (>8) were treated with a median of 4 courses of antimicrobials, compared with 3 in patients with a SOFA score <8. The median total exposure days in patients with lower SOFA scores (<6) was 5, this increased to 7 in patients with SOFA scores between 8 and 11 but then reduces to 4 days in patients with SOFA scores >13. A similar pattern is seen in the cumulative exposure days. This could be because patients with higher levels of organ dysfunction are at greater risk of death.

In terms of comorbidities, patients with a higher Elixhauser comorbidity index (>14) were treated with more courses (4, IQR 3-6) over a greater number of total exposure days (7, IQR 4-11) and cumulative exposure days (15, IQR 7-26) than patients within the lowest index group who received a median of 3 courses (IQR 2-4) over 5 total exposure days (IQR 3-8) and 9 cumulative exposure days (IQR 5-18).

Table 2 shows the mortality rates and length of stay of the full cohort and subgroups. 14% of all patients died in ICU, however in the subgroup of explicit ICD patients this figure was 34 %. For the whole cohort the overall 30-day mortality rate was 22% but ranged from 29% (Angus criteria) to 44% (explicit code criteria) in the subgroups. 1-year mortality rates ranged from 35 – 55 %, again the patients who had an explicit sepsis ICD-9 code had higher longer-term mortality. Figure 4 shows the 30-day survival Kaplan-Meier curves for the cohort and subgroups. The median ICU length of stay also increased as the subgroup size decreased, ranging from 2.4 days in the whole cohort to 3.7 days in the explicit code criteria subgroup.

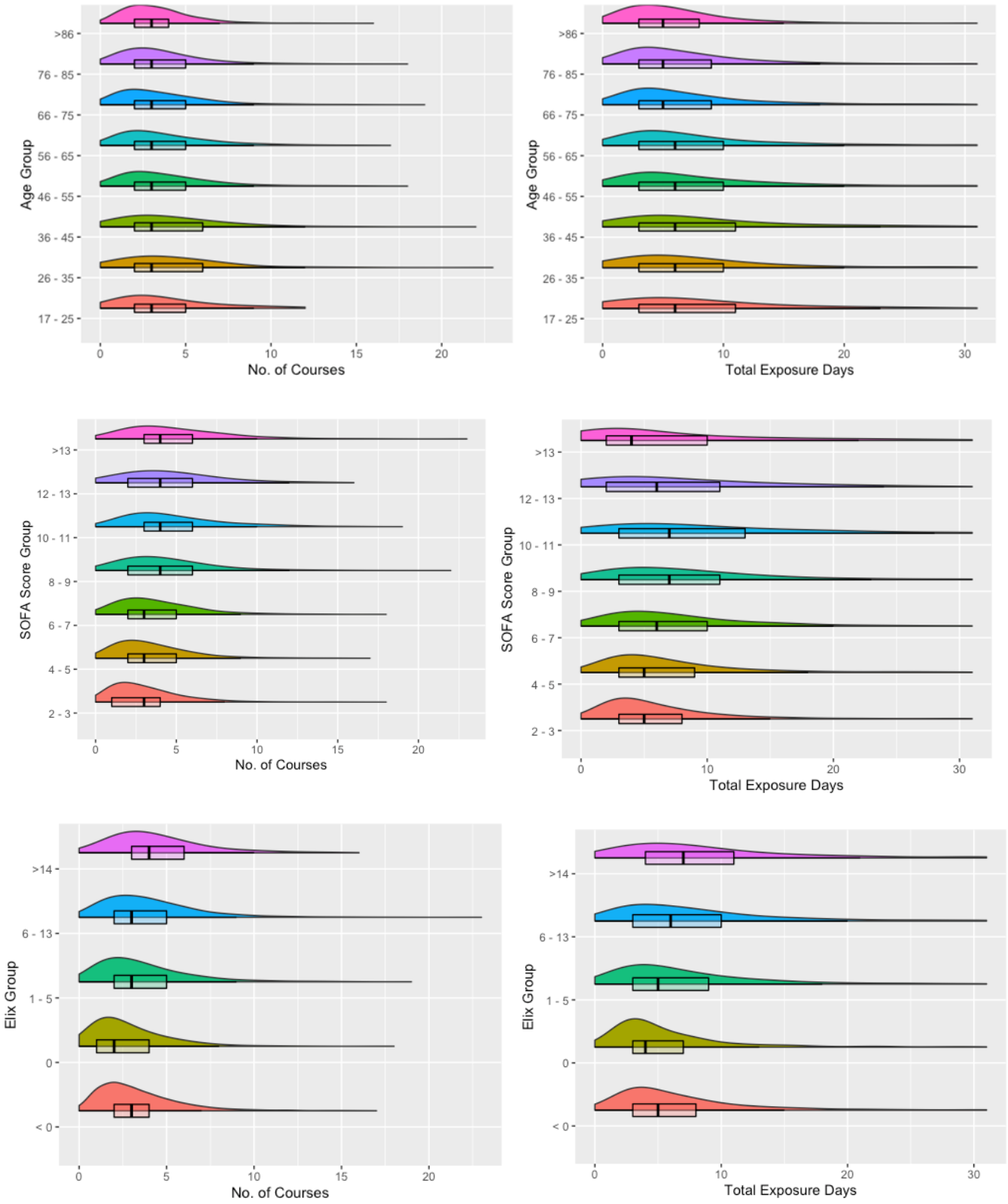


Figure 5.3 *Distribution of the number of antimicrobial courses and number of exposure days by age, SOFA score and Elixhauser comorbidity index*

	All Sepsis-3 patients	Angus ICD criteria	Martin ICD criteria	Explicit ICD criteria
Mortality (%)				
ICU	1,209 (14%)	874 (19%)	613 (25%)	537 (34%)
Hospital	1,576 (18%)	1,119 (25%)	773 (31%)	646 (41%)
30-day	1,924 (22%)	1,319 (29%)	867 (35%)	688 (44%)
90-day	2,429 (28%)	1,638 (36%)	1,038 (42%)	794 (50%)
1-year	3,036 (35%)	1,951 (43%)	1,181 (48%)	866 (55%)
ICU Length of stay (days)				
Median	2.4 (1.4, 5.0)	3.3 (1.8, 7.3)	3.0 (1.7, 7.2)	3.7 (1.9, 8.5)
<2	3,479 (40%)	1,399 (31%)	801 (32%)	434 (28%)
2-4	2,410 (28%)	1,151 (26%)	639 (26%)	379 (24%)
5-7	1,289 (15%)	776 (17%)	396 (16%)	274 (17%)
>7	1,461 (17%)	1,178 (26%)	638 (26%)	488 (31%)
Hospital Length of Stay (days)				
Median	8.0 (4.8, 13.8)	9.9 (5.8, 17.4)	9.3 (5.1, 17.6)	9.3 (5.0, 17.4)
<4	1,639 (19.0%)	653 (14.5%)	417 (16.9%)	290 (18.4%)
5-8	2,652 (30.7%)	1,171 (26.0%)	677 (27.4%)	410 (26.0%)
9-12	1,720 (19.9%)	847 (18.8%)	419 (16.9%)	262 (16.6%)
>13	2,628 (30.4%)	1,833 (40.7%)	961 (38.8%)	613 (38.9%)

Table 5.2 *Mortality and length of stay summary*

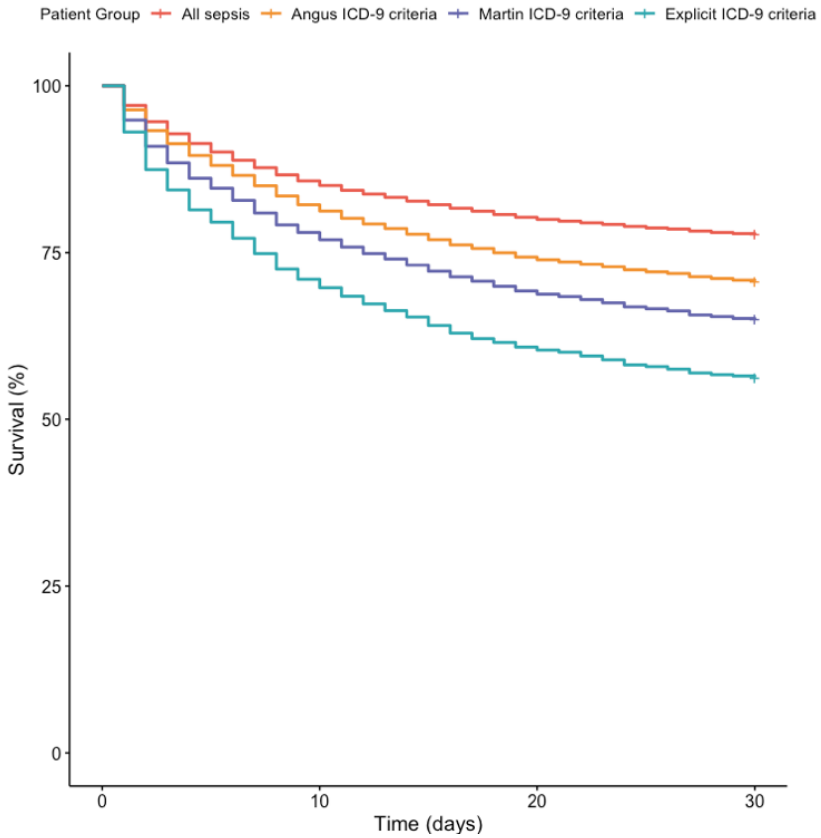


Figure 5.4 *Kaplan-Meier survival curves for 30-day survival of the full cohort and subgroups*

In the full cohort of sepsis patients and the Martin criteria subgroup the mortality rate in female patients was slightly higher than male patients (Table 3, 22.7 vs 21.9% and 35.3 vs 34.8%, respectively), however, for the Angus and explicit criteria subgroups male patients had the higher mortality (29.8 vs 28.7% and 44.3 vs 43.0%, respectively). In terms of ethnicity mortality rates varied slightly across the cohort and subgroups. For the full cohort the lowest mortality rate was in Hispanic patients (19.3%), however, in the explicit criteria subgroup Hispanic patients had the highest mortality rates (47.8%).

For the full cohort the median age was higher in patients who died than those who survived (66.3 vs 73.0 years), which was similar across the subgroups. Similarly, patients in the full cohort who died had a higher SOFA score and higher Elixhauser comorbidity index on admission to ICU than surviving patients (SOFA 4 vs 7, Elixhauser 2 vs 8) and this was mirrored in the subgroups.

Surviving patients received a median of 6 total days' worth of antibiotics (IQR 3-10), compared with 4 days in the non-survivor's group (IQR 2-8). Cumulative antimicrobial exposure was slightly higher in patients who died (11, IQR 5-21) than those who survived (10, 5-20). The median number of courses prescribed to patients who survived the 30-day follow-up period was 3 (IQR 2-5), compared with 4 (IQR 2-5) for patients who died. For the patient subgroups the number of antimicrobial courses prescribed increased, however, there wasn't a difference between patients who survived or died. In terms of the number of exposure days during the follow-up, this also increased in the smaller subgroups, with patients who survived having a higher number of total and cumulative exposure days than those who died.

	All Sepsis-3 Patients		Angus ICD criteria		Martin ICD criteria		Explicit ICD criteria	
	Survived	Died	Survived	Died	Survived	Died	Survived	Died
No. of ICU admissions	6,715	1,924	3,185	1,319	1,607	867	887	688
Gender								
Female	2963 (77.3%)	871 (22.7%)	1492 (71.3%)	602 (28.7%)	707 (64.7%)	386 (35.3%)	401 (57.0%)	302 (43.0%)
Male	3752 (78.1%)	1053 (21.9%)	1693 (70.2%)	717 (29.8%)	900 (65.2%)	481 (34.8%)	486 (55.7%)	386 (44.3%)
Ethnicity								
White	4951 (78.0%)	1400 (22.0%)	2347 (70.9%)	964 (29.1%)	1186 (64.7%)	646 (35.3%)	659 (56.4%)	510 (43.6%)
Black	671 (79.4%)	174 (20.6%)	328 (72.1%)	127 (27.9%)	164 (69.2%)	73 (30.1%)	86 (58.5%)	61 (41.5%)
Hispanic	246 (80.6%)	59 (19.3%)	106 (72.6%)	40 (27.4%)	53 (63.9%)	30 (36.1%)	24 (52.2%)	22 (47.8%)
Other	847 (74.4%)	291 (25.6%)	404 (68.2%)	188 (31.8%)	204 (63.4%)	118 (36.6%)	118 (55.4%)	95 (44.6%)
Age (years)	66.3 (53.8, 78.7)	73.0 (60.3, 83.2)	67.5 (54.6, 79.7)	73.6 (60.4, 83.3)	66.9 (54.3, 79.5)	72.3 (60.4, 82.9)	67.2 (55.1, 80.0)	72.2 (60.5, 83.0)
SOFA score	4 (3, 6)	7 (4, 10)	5 (3, 7)	8 (5, 11)	5 (4, 8)	9 (6, 12)	6 (4, 9)	9 (6, 13)
Elixhauser comorbidity index	2 (-1, 7)	8 (3, 12)	4 (0, 9)	8 (4, 13)	5 (0, 10)	9 (4, 13)	6 (0, 10)	9 (4, 14)
No. of anti-microbial courses per patient	3 (2-5)	4 (2-5)	4 (3, 6)	4 (3, 6)	4 (3, 6)	4 (3, 6)	5 (3, 7)	5 (3, 6)
No. of exposure days in 30-days	6 (3-10)	4 (2-8)	8 (5, 13)	5 (3, 10)	8 (6, 14)	6 (3, 10)	9 (6, 15)	5 (3, 10)
Cumulative abx exposure in 30-days	10 (5-20)	11 (5-21)	16 (9, 28)	14 (7, 25)	18 (11, 32)	15 (8, 28)	20 (12, 35)	15 (8, 28)

Table 5.3 *Summary of survival by demographic and antibiotic use*

Kaplan-Meier curves are shown in Figure 5, below, stratifying by six characteristics. The curves show that there was only a small difference in survival between males and females (5b) during the 30-day follow-up period, additionally the curves for ethnicity were also similar (5c). Older patients had lower survival rates (5a), as did patients admitted as an emergency compared with urgent or elective cases (5b). Patients with a higher SOFA score on admission to ICU have lower survival over the follow-up (5e), as do patients with a higher Elixhauser comorbidity index (5f).

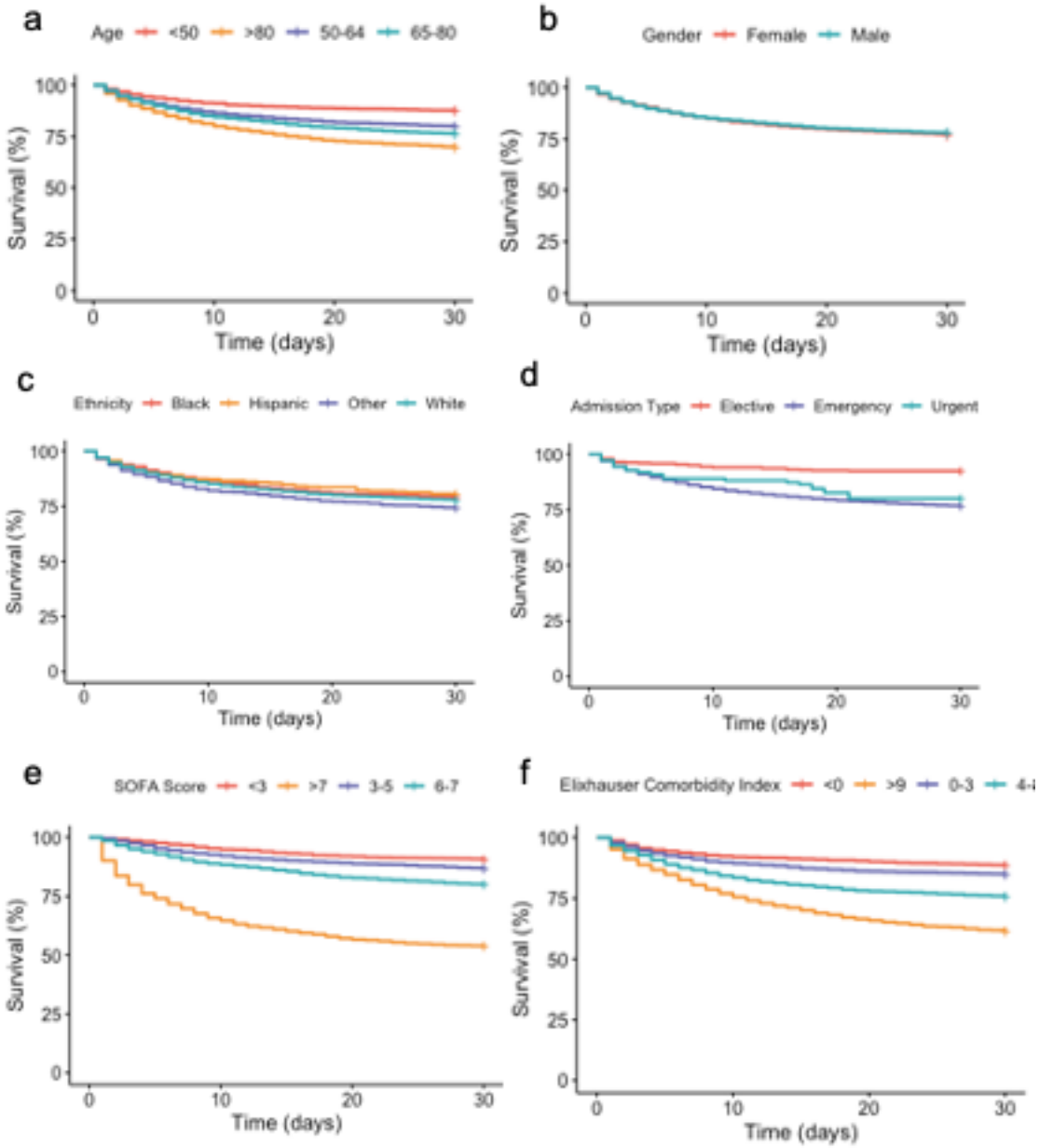


Figure 5.5 *Kaplan-Meier curves of 30-day survival for patients admitted to ICU with sepsis*
Curves are stratified by key variables including age (a), gender (b), ethnicity (c), admission type (d), SOFA score (e) and Elixhauser comorbidity index (f).

Table 4 shows the hazard ratios and 95% confidence intervals from the unadjusted and adjusted Cox regression analysis performed using the full cohort. The adjusted HR for age was 1.02 (95% CI 1.02, 1.02), indicating that increasing age was associated with a higher risk of mortality. Males had a reduced risk of mortality compared to females (HR 0.92, 95% CI 0.84-1.01). For ethnicity Hispanic (HR 1.26, 95% CI 0.94-1.70), white (HR 1.14, 95% CI 0.98-1.34) and other (HR 1.2, 95% CI 0.99-1.45) patients had higher HRs compared to black patients, however, none of these were significant in the adjusted model. Patients admitted as an emergency (HR 2.4, 95% CI 1.73-3.33) or urgent (HR 1.88, 95% CI 1.11-3.19) case were at greater risk of mortality than those admitted for elected procedures.

The Elixhauser comorbidity index and SOFA score were both included in the model as time-varying coefficients, with a parametric function of time (√time), in order to satisfy the proportional hazards assumption. In the adjusted model, at time 0 the HR for the Elixhauser comorbidity index was 0.99 (95% CI 0.97-1.01), but this changed over the √time (HR 1.02, 95% CI 1.02, 1.03). For the SOFA score, at time 0 the HR was 1.33 (95% CI 1.30-1.37), however this decreased over the time period with the HR for the function of time at 0.96 (0.95-0.97). Therefore, the effect of the comorbidity index on mortality risk increased over time, however, the effect of the SOFA score on mortality risk decreased throughout follow-up.

The adjusted HR for the number of antimicrobials prescribed was 1.20 (95% CI 1.17, 1.22), so patients who received more antimicrobials were more likely to die during the 30-day follow-up. However, in terms of the number of exposure days the adjusted HR was 0.92 (95% CI 0.90-0.93), meaning that patients receiving antimicrobials on more days had a lower risk of mortality.

Characteristic	Unadjusted HR	95% CI	P-value	Adjusted HR	95% CI	P-value
Age (years)	1.02	1.02, 1.02	<0.001	1.02	1.02, 1.02	<0.001
Gender (ref Female)						
Male	0.96	0.88, 1.05	0.065	0.92	0.84, 1.01	0.086
Ethnicity (ref Black)						
Hispanic	0.93	0.70, 1.26	0.7	1.26	0.94, 1.70	0.12
Other	1.28	1.06,1.55	0.009	1.2	0.99, 1.45	0.056
White	1.08	0.92, 1.26	0.3	1.14	0.98, 1.34	0.094
Admission Type (ref Elective)						
Emergency	3.31	2.39, 4.58	<0.001	2.4	1.73, 3.33	<0.001
Urgent	2.78	1.64, 4.72	<0.001	1.88	1.11, 3.19	0.02
Elixhauser Comorbidity Index	1.04	1.03,1.06	<0.001	0.99	0.97, 1.01	0.2
tt(Elixhauser Comorbidity Index)	1.01	1.01, 1.02	<0.001	1.02	1.02, 1.03	<0.001
SOFA Score	1.34	1.31, 1.38	< 0.001	1.33	1.30, 1.37	<0.001
tt(SOFA score)	0.96	0.96, 0.97	<0.001	0.96	0.95, 0.97	<0.001
No. of antimicrobials prescribed	1.18	1.16,1.20	<0.001	1.2	1.17, 1.22	<0.001
No. of exposure days	1.01	1.00, 1.02	0.046	0.92	0.90, 0.93	<0.001

Table 5.4 *Hazard ratios with 95% confidence intervals (CIs) for unadjusted and adjusted Cox proportional hazard model*

5.5 Discussion

One of the challenges in sepsis research is identifying patients with the condition and as sepsis is difficult to spot clinically it is also difficult to code for in medical records. Using code-based criteria as well as the sepsis-3 criteria in this study resulted in 4 cohorts of differing sizes and sepsis severity. There were 8,639 incident ICU admissions meeting the sepsis-3 criteria (37% of the admissions in the MetaVision database), which is quite high in comparison to another study which reported around 18% of ICU patients admitted with sepsis. They didn't use the exact sepsis-3 criteria to identify sepsis though and those reported figures are an average across multiple centres and countries.

Of the patients in our full cohort, 52% meet the Angus code criteria, 29% meet the Martin code criteria and only 18% of patients have an explicit ICD-9 code for severe sepsis or septic shock. In a multi-centre study, also in the US, Rhee et al [17] identified a cohort of 173,690 patients who met adapted sepsis-3 criteria, 64% of whom met the Angus criteria and 31% who

met the explicit code criteria. This is higher than found in our study, however, this could be due to the differences in sepsis-3 criteria used and that their study used hospital-wide admissions, not just ICU. Patients in the smaller cohorts are slightly older, have higher a comorbidity burden and a higher SOFA score than in the overall cohort. These patients also experience lower survival rates. Other studies have also found differences in incidence and cohort size when using different selection criteria and have found code-based strategies are biased to a more severely ill patient population [17,1819]. An advantage of the present study, therefore, is the ability to use both type of method to identify patients.

The majority of antimicrobials (94%) prescribed in the 30-day follow up period were antibiotics, with vancomycin accounting for 23% of all prescriptions. 97.9% of patients in our cohort received an antibiotic, 9.9% received an antifungal and 5.9% were prescribed antivirals. The ICON study reported similar proportions of patients receiving antibiotics (99.4%) and antivirals (6.5%) but much larger use of antifungal drugs (19.6%) [7]. Their figures represent the global picture though. A multicentre study in Spain described empiric antibiotic therapy in patients with severe sepsis, finding that β-lactams were the most frequently prescribed [20]. This was also seen in a large international point prevalence study of ICU patients where the majority of patients with an infection were treated with β-lactams [21].

Vancomycin is an antibiotic frequently used to treat hospital-acquired infections such as Methicillin-resistant *Staphylococcus aureus* (MRSA)[22]. Its use in this study seems high in comparison to the UK but this could be due to differences in antimicrobial resistance patterns. The ICON audit found isolates of MRSA were more common in North America (12.8% vs 6.1%) than Western Europe [7]. A study in another US hospital found 28.2% of prescriptions were for vancomycin, which is higher than in our study (22.5% of prescriptions) [15].

The sepsis cohort identified in the study by Rhee et al[17] had a similar age (mean 66.5 years) to our cohort as well as a similar proportion of males and females (males 57.6%, females 42.4%). Both ICU and hospital length of stay was longer in their study. Hospital mortality was higher in our cohort (18% vs 15%) however this might be due to that study using hospital-wide medical records, not just ICU. The ICON study, an international multi-centre audit of ICU sepsis patients, reported an average ICU mortality of 18.5% and hospital mortality of 25.2% across North America [7].

Other studies have found that increasing age, presence of comorbidities and increasing disease severity are associated with higher mortality [7,23]. Our study found that increased age had only a small increased associated risk in mortality. A higher level of disease severity (SOFA score) was significantly associated with increased risk of mortality, although this

decreased over the 30-day period. In terms of comorbidities, at time 0 the Elixhauser index was not significantly associated with mortality however the hazard ratio did increase over time.

Surviving patients received a lower number of antimicrobial courses than those who died, and the Cox model results showed increasing the number of courses was associated with a higher risk of mortality. This may be because they were treated with an antimicrobial appropriate for the infecting microorganism which has been shown to be associated with lower mortality [24]. Or this could be due to these patients being more likely to have lower levels of organ dysfunction on admission or fewer underlying comorbidities.

In terms of the number of days exposed to antimicrobials the results are mixed. The number of total exposure days increases as comorbidity levels increase, but patients with a SOFA score in the mid-range (8-11) are exposed on more days than patients with low or very high scores. This may be because these patients with a high SOFA score are at a greater risk of dying early. The Cox regression results (where this competing risk of death on antimicrobial use has been taken into account) indicate that patients exposed on more days are at a lower risk of mortality. The link therefore between disease severity, number of days exposed to antimicrobials and mortality is not clear from this study.

There are risks associated with antibiotic use, such as increased risk of secondary infection, development of resistance to antibiotics and interactions with other drugs [25]. These risks could increase with the use of different antimicrobials. Stevens et al [15] found that increased exposure to antibiotics, both in terms of the number of different antimicrobials and exposure days, was associated with a greater risk of developing *C difficile* infection.

5.5.1 Limitations

One of the limitations of this study is that data was only available for patients admitted to ICU, this may have led to a sicker cohort with higher mortality and not be representative of all sepsis patients. Additionally, the MIMIC III database only contains data from a single centre, so the results from this study may not be generalisable to other settings.

As the MIMIC database primarily consists of ICU medical records the data around drug use in the database is not recorded consistently throughout the patient's hospital admission. Prescriptions data is available for the full admission and does include a start date and end date, however, how frequently drugs are administered is only available for IV drugs given to patients in the ICU. Additionally, once patients were discharged there were no community prescriptions data available. This meant that calculating standardised exposure rates such as

the defined daily dose wasn't possible for the follow-up period. Assumptions were made when calculating the patient's exposure to antibiotics, that the patients were exposed on each day that a prescription was valid for, and if a patient was discharged from the ICU to another hospital ward then the prescription remained valid and the patient continued to be exposed. This is a type of information bias.

These issues highlight the limitations of using observational electronic health record data to address this kind of research question. As well as immortal time bias and information bias, mentioned previously, an additional risks of bias to consider is around confounding. Baseline disease severity and comorbidity levels are potential confounders for the relationship between antibiotic exposure and mortality, although we have adjusted for these in the analysis it is not possible to draw causal conclusions from the results. We could have stratified the cohort by sepsis severity and comorbidity levels and analysed them separately. In order to reduce the effects of confounder bias and address the causal relationship between antibiotic exposure and death a prospective randomised control trial would be better suited, with additional inclusion/exclusion criteria applied and patients randomly assigned to different pre-defined treatment regimens. This approach would enable antibiotic exposure to be calculated more accurately without assumptions being made.

5.5.2 Conclusion

Sepsis patients are exposed to high levels of antimicrobials, both in terms of number of courses prescribed and number of days of exposure, with antibiotics accounting for the majority of antimicrobials used. Patients had high levels of organ dysfunction and comorbidities which can increase the risk of mortality. Cox proportional hazards regression showed that patients who received a lower number of antimicrobials but have more days of exposure to antibiotics are at a lower risk of mortality within 30-days of ICU admission.

5.6 References

1. Rudd, K. E. *et al.* Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *The Lancet* **395**, 200–211 (2020).

2. Singer, M. *et al.* The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* **315**, 801 (2016).

3. Prescott, H. C., Langa, K. M., Liu, V., Escobar, G. J. & Iwashyna, T. J. Increased 1-Year Healthcare Use in Survivors of Severe Sepsis. *Am J Respir Crit Care Med* **190**, 62–69 (2014).

4. Shankar-Hari, M. & Rubenfeld, G. D. Understanding Long-Term Outcomes Following Sepsis: Implications and Challenges. *Curr Infect Dis Rep* **18**, (2016).

5. World Health Organisation. *Global Action Plan on Antimicrobial Resistance*. *Sixty-eighth World Health Assembly (document WHA68/2015/REC/1, Annex 3)* (2015) doi:10.1128/microbe.10.354.1.

6. Rhodes, A. *et al.* Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med* **43**, 304–377 (2017).

7. Sakr, Y. *et al.* Sepsis in Intensive Care Unit Patients: Worldwide data from the ICON audit. *Open Forum Infect Dis* **5**, (2018).

8. Johnson, A. *et al.* MIMIC-III, a freely accessible critical care database. *Sci Data* **3**, 1–9 (2016).

9. Johnson, A. E. W., Stone, D. J., Celi, L. A. & Pollard, T. J. The MIMIC Code Repository: enabling reproducibility in critical care research. *Journal of the American Medical Informatics Association* **25**, 32–39 (2018).

10. Johnson, A. E. W. *et al.* A Comparative Analysis of Sepsis Identification Methods in an Electronic Database. *Crit Care Med* **46**, 1 (2018).

11. Vincent, J.-Louis. *et al.* The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med* **22**, 707–710 (1996).

12. Angus, D. C. *et al.* Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* **29**, 1303–1310 (2001).

13. Martin, G. S., Mannino, D. M., Eaton, S. & Moss, M. The Epidemiology of Sepsis in the United States from 1979 through 2000. *New England Journal of Medicine* **348**, 1546–1554 (2003).

14. Charani, E. *et al.* Antibiotic prescribing in general medical and surgical specialties: a prospective cohort study. *Antimicrobial Resistance & Infection Control* **8**, 151 (2019).

15. Stevens, V., Dumyati, G., Fine, L. S., Fisher, S. G. & van Wijngaarden, E. Cumulative Antibiotic Exposures Over Time and the Risk of Clostridium difficile Infection. *Clinical Infectious Diseases* **53**, 42–48 (2011).

16. Zhang, Z., Reinikainen, J., Adeleke, K. A., Pieterse, M. E. & Groothuis-Oudshoorn, C. G. M. Time-varying covariates and coefficients in Cox regression models. *Ann Transl Med* **6**, 121 (2018).

17. Rhee, C. *et al.* Incidence and Trends of Sepsis in US Hospitals Using Clinical vs Claims Data, 2009-2014. *JAMA* **318**, 1241 (2017).

18. Mariansdatter, S. E., Eiset, A. H., Søgaard, K. K. & Christiansen, C. F. Differences in reported sepsis incidence according to study design: a literature review. *BMC Med Res Methodol* **16**, 1–13 (2016).

19. Whittaker, S.-A. *et al.* Severe sepsis cohorts derived from claims-based strategies appear to be biased toward a more severely ill patient population. *Critical care medicine* **41**, 945–53 (2013).

20. A., D.-M. *et al.* Antibiotic prescription patterns in the empiric therapy of severe sepsis: Combination of antimicrobials with different mechanisms of action reduces mortality. *Critical Care* **16**, R223 (2012).

21. Vincent, J. L. *et al.* Prevalence and Outcomes of Infection among Patients in Intensive Care Units in 2017. *JAMA - Journal of the American Medical Association* **323**, 1478–1487 (2020).

22. Rybak, M. *et al.* Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *American Journal of Health-System Pharmacy* **66**, 82–98 (2009).

23. Shankar-Hari, M., Harrison, D. A., Rubenfeld, G. D. & Rowan, K. Epidemiology of sepsis and septic shock in critical care units: comparison between sepsis-2 and sepsis-3 populations using a national critical care database. *Br J Anaesth* **119**, 626–636 (2017).

24. Martínez, M. L., Plata-Menchaca, E. P., Ruiz-Rodríguez, J. C. & Ferrer, R. An approach to antibiotic treatment in patients with sepsis. *J Thorac Dis* **12**, 1007–1021 (2020).

25. Denny, K. J., De Waele, J., Laupland, K. B., Harris, P. N. A. & Lipman, J. When not to start antibiotics: avoiding antibiotic overuse in the intensive care unit. *Clinical Microbiology and Infection* (2019) doi:10.1016/J.CMI.2019.07.007.

5.7 Supplementary materials

	Number of Courses	Total Exposure Days	Cumulative Exposure Days
Age Group			
17 - 25	3 (2, 5)	6 (3, 11)	12 (5, 22)
26 - 35	3 (2, 6)	6 (3, 10)	12 (5, 23)
36 - 45	3 (2, 6)	6 (3, 11)	12 (5, 27)
46 - 55	3 (2, 5)	6 (3, 10)	11 (5, 23)
56 - 65	3 (2, 5)	6 (3, 10)	11 (5, 23)
66 - 75	3 (2, 5)	5 (3, 9)	10 (5, 20)
76 - 85	3 (2, 5)	5 (3, 9)	10 (5, 18)
>86	3 (2, 4)	5 (3, 8)	9 (5, 16)
SOFA Score			
2 - 3	3 (1, 4)	5 (3, 8)	8 (4, 16)
4 - 5	3 (2, 5)	5 (3, 9)	10 (5, 19)
6 - 7	3 (2, 5)	6 (3, 10)	12 (6, 22)
8 - 9	4 (2, 6)	7 (3, 11)	14 (7, 26)
10 - 11	4 (3, 6)	7 (3, 13)	16 (7, 31)
12 - 13	4 (2, 6)	6 (2, 11)	13 (6, 27)
>13	4 (3, 6)	4 (2, 10)	11 (5, 29)
Elixhauser Score			
< 0	3 (2, 4)	5 (3, 8)	9 (5, 18)
0	2 (1, 4)	4 (3, 7)	6 (3, 13)
1 - 5	3 (2, 5)	5 (3, 9)	10 (5, 19)
6 - 13	3 (2, 5)	6 (3, 10)	12 (6, 24)
>14	4 (3, 6)	7 (4, 11)	15 (7, 26)

Table ST5.1 *Antimicrobial exposure stratified by age group, SOFA score and Elixhauser comorbidity index*

Chapter 6 - Long term outcomes in sepsis – a retrospective study using linked primary and secondary care data

6.1 Abstract:

Background: Sepsis is a serious condition with high short-term mortality and risk of longer-term mortality and adverse health impact, such as cardiovascular disease and cognitive function decline. Previous studies have found that a combination of pre-sepsis and acute-sepsis factors affect the risk of long-term outcomes in sepsis survivors, however, there are none differentiating between hospital- and community-acquired sepsis. Additionally, studies estimating the burden of healthcare use post-sepsis have focused on acute hospital admissions and use of long-term care facilities, with none looking at the impact on primary care services.

Aims: To evaluate long-term outcomes in survivors of community- and hospital-acquired sepsis, in terms of mortality, comorbidities and use of primary care services.

Methods: Patients with sepsis were identified in HES records using ICD-10 codes, divided into community-acquired and hospital-acquired sepsis and matched with either community based controls from CPRD records or hospital based controls from HES records. Data around comorbidities, primary care antibiotic use and common infection consultations were extracted for the 3-year period either side of the sepsis admission. Mortality data was linked from ONS and readmission data from HES records. Kaplan-Meier estimates, cumulative incidence function estimates and regression modelling was done, with prior antibiotic use and comorbidities as potential risk factors.

Results: There were 71,330 community-acquired sepsis cases and 6,064 hospital-acquired sepsis cases who survived their sepsis admission, matched with 417,010 and 32,539 controls, respectively. Cumulative incidence rates for 1-year all-cause mortality were 35.2% (95% CI 34.8-35.5%) for community-sepsis cases and 46.0% (95% CI 44.7-47.3%) for hospital-sepsis cases, and incidence of all-cause hospital readmission (adjusting for death as competing risk) was 69.1% (95% CI 68.7-69.4%) for community-sepsis and 68.7% (95% CI 67.5-69.9%) for hospital sepsis. Cox proportional hazard modelling showed prior antibiotic use and comorbidities increased risk of survival in both cohorts but the effects were greater in the community-acquired patients. Comparing antibiotic use in the pre- and post-sepsis periods, community-acquired sepsis patients had higher rates than hospital-acquired sepsis patients

prior to sepsis. However, in the post-sepsis period, the rates were similar between the groups and higher than the rates prior to sepsis for both groups.

Conclusion: Patients who survive a sepsis episode have a higher risk of long-term mortality than matched controls, have increased levels of comorbidity and increased antibiotic use. Increased antibiotic use in the period prior to sepsis and higher comorbidity levels was significantly associated with an increased risk of mortality and readmission in community-acquired sepsis, but less so in hospital-acquired.

6.2 Introduction:

Sepsis is a serious and potentially life-threatening condition that can cause significant damage to organs and tissues around the body. Estimates of in-hospital mortality rates for sepsis patients range from 5 - 42.5%[1], and patients who survive an episode of sepsis can have a higher risk of longer-term mortality and hospital readmission[2–5]. Risk factors associated with mortality and readmission are a combination of factors relating to their sepsis episode and those around their general health before sepsis[4].

There is increasing evidence that sepsis survivors have an increase in the risk of impaired cognitive function, cardiovascular events and other comorbidities, as well as mental health conditions including anxiety and depression[5,6]. A 2014 US study concluded that survivors of severe sepsis have increased use of healthcare in the year following hospitalisation, however they only included use of in-patient facilities not community services. Another similar US study looked at care use on discharge from hospital after a sepsis episode, they included home health services and rehabilitation, as well as long term acute care, however they also did not include primary care interactions and they only measured the outcome on discharge without following up[7]. A third study by Liu et al [8] did include outpatient service use but only reported the results as overall healthcare utilisation including in-hospital care as well.

A 2017 study followed up patients after a stay in ICU in Scotland and reported a decrease in patient reported physical and mental scores, and although this was not specific to sepsis patients the cohort will have included patients with sepsis[9]. There are no UK studies using routinely collected electronic health record data to follow-up sepsis patients in primary care, and none that compare community-acquired sepsis patients to hospital-acquired sepsis patients, or to respective control groups.

There is some evidence that the impaired immune response experienced in sepsis patients can be prolonged, which could make them more vulnerable to recurrent infections and therefore increase their use of antibiotics.

The overall aim of this study was to evaluate the long-term outcomes following a sepsis episode using linked primary and secondary care data, and to include comparisons of patients who had community-acquired sepsis. Specific objectives were to determine (i) the hospital readmission rates and its predictors following a sepsis episode at 1- and 3-year time points, (ii) the mortality rates and its predictors after discharge from hospital at 1- and 3-year time points, (iii) if patients develop additional comorbidities after sepsis, (iv) if patients become higher users of antibiotics following sepsis and (v) if patients are more vulnerable to common infection following sepsis.

6.3 Methods

6.3.1 Data Source

This study used anonymised, routinely collected electronic health record data from the Clinical Practice Research Datalink (CPRD). CPRD Aurum contains records from around 19 million patients across 738 general practices (GPs)[10]. CPRD GOLD covers approximately 5 million patients from 674 practices across the UK[11]. These GP records were linked with Hospital Episode Statistics (HES) records, covering all hospital admissions in England, Office for National Statistics (ONS) mortality data and Index of Multiple Deprivation (IMD) scores, which is published by the UK government and is a score consisting of numerous indicators. It is calculated by lower super output area and areas are then ranked from least to most deprived, and grouped into quintiles.

6.3.2 Setting

Patients were identified in HES records with a hospital admission for sepsis between 2000 and 2020, using ICD-10 codes (see appendix for code lists), then their GP records for the prior and following period extracted.

6.3.3 Participants

Eligible patients with a sepsis admission over the age of 65 were identified. Where patients had multiple sepsis admissions the earliest was identified and patients were excluded if they had a historic record of sepsis in GP records, if the admission did not fall within their GP

registration period or if they had less than 1 year of GP records prior to hospital admission. Restricting the age of patients was to reduce the sample size and the data extract from CPRD, and to make use of readily available data for patients in this age group (see Methods section 3.3 for more details). They were divided into community- and hospital- acquired sepsis based on when their sepsis episode began in relation to their admission (using a cut-off of 2 days), then matched with either community controls or hospital patient controls. Controls for community-acquired sepsis cases were identified in primary records and matched on GP, age (± 5 years), sex and calendar time. Controls for hospital-acquired sepsis cases were identified in HES records with a non-infection related diagnosis, and matched on age (± 5 years), sex and calendar time. Both groups were matched on a ratio of 1:6. Potential controls with a GP record of sepsis or less than 1 year of GP records were excluded.

For this study additional criteria were applied, to remove patients who did not survive their initial sepsis episode. Any sepsis patients or hospital controls who died during their hospital stay were removed, as well as any community control patients who died during the same period that their associated sepsis case was in hospital. Any controls matched with sepsis cases who died were also removed from the cohort, along with any cases and controls who did not have a discharge date recorded for their hospital stay.

6.3.4 Variables

The primary outcome of interest was all-cause mortality, at 1 and 3-year time-points. Date of death was extracted from ONS mortality data and linked via the unique patient id. The end of observation date in GP records was used to censor patients if they did not have the maximum 3 years of follow-up.

Secondary outcomes were all-cause hospital readmission, at 1 and 3-year time points, identified in HES records. Additionally, records of GP consultations for common infections (upper respiratory tract infection (URTI), lower respiratory tract infection (LRTI), urinary tract infection (UTI), sinusitis, cough/cold, pneumonia, skin infection, otitis media) and GP antibiotic prescriptions were extracted for a maximum of 3 years before and after the index hospital admission. Where patients had more than one infection consult or antibiotic prescription on the same day, only one was counted. Finally, the Charlson comorbidity score was calculated for each patient and compared to the score before the index hospital admission.

The covariates of interest are basic demographics and comorbidities. All variables except IMD score were extracted from GP records using lists of Read or SNOMED codes, which can be

found in the appendix. IMD score was linked through unique patient id and was recorded by quintiles where 1 are the least deprived and 5 are the most deprived patients. Age was reported as a continuous variable and also grouped for certain analyses (60-74, 75-84, 85-94 & >95 years), sex was recorded as either male or female, Body Mass Index (BMI) was recorded as kg/m^2 and grouped as low (<18.5), normal (18.5-24), overweight (25-30) and obese (>30) and smoking status categorised as current, ex- or non-smoker. The number of patients with missing values was recorded.

Individual comorbidities (cancer, cerebrovascular disease (CVD), chronic obstructive pulmonary disease (COPD), heart failure, dementia, diabetes, HIV, liver disease, moderate/severe renal disease, peripheral vascular disease (PVD), autoimmune disease, coronary heart disease (CHD), skin ulcers, hypertension and deep vein thrombosis (DVT)) were recorded as binary variables. The Charlson comorbidity score was calculated for each patient and grouped as 0, 1-2, 3-4, 5-6 and 7+ using a pre-defined score. These variables were extracted before the index sepsis admission and up to 3-years after.

6.3.5 Statistical methods

The amount of follow-up time was calculated for each patient from their index date to either their date of death, date of end of observation in CPRD or a maximum of 3 years. The index date for all sepsis cases and the hospital controls was the date of discharge from hospital, for the community controls the index date was the same as for their associated sepsis case.

Summary statistics were created for the cohort and sub-cohorts. Continuous variables were reported as median with interquartile range, and also grouped to show the distribution. All discrete variables were reported as the number of patients and %. Differences in proportions of categorical variables were tested using Chi-squared tests and differences in continuous variables with Wilcoxon rank-sum tests.

Crude mortality and readmission rates were calculated at both a 1-year and 3-year time points. Time to death and first hospital readmission were modelled using cumulative incidence plots, censoring patients if they reached the end of their CPRD registration period. For readmission the analysis was adjusted for death as a competing risk. Patients were stratified by case and control groups, demographic factors (age, BMI, IMD, sex, Charlson comorbidity score) and by their antibiotic use prior to index. Incidence probabilities were reported with 95% confidence intervals (CI).

Multivariable models for mortality and hospital readmission outcomes, at 1- and 3-year time points, were performed adjusting for demographic and comorbid variables. For the mortality outcome Cox proportional hazards regression models were used and for the hospital readmission outcome a Fine-Grey model was used, to account for death as a competing risk. Unadjusted and fully adjusted hazard ratios were reported, with 95% confidence intervals and p-values. Separate models were run in the community and hospital patient cohorts, stratifying by Aurum/Gold cohort variables.

The number of primary care antibiotics and consults for common infections was calculated and compared, and the most frequent types of infection and antibiotic identified. Infection and prescription rates were calculated per 1,000 patients per week and plotted for the pre and post sepsis period, and a rolling 8 week average calculated. Kaplan-Meier analysis was performed to model the time to first antibiotic prescription, to take into account patients who either died or were lost to follow up.

The results presented in the main paper are for the Gold and Aurum patients together, for separate results please see the supplementary materials.

Software: All analyses were performed in R, version 4.0.2. Particular packages used were *survival* (Cox proportional hazards model), *tidycmprsk* (cumulative incidence plots and Fine-Grey model), *survminer* (Kaplan-Meier curves) and *tidyverse*.

6.4 Results

6.4.1 Patient characteristics

There were 55,346,914 patients in the CPRD source files, of whom 44,665,523 were eligible for linkage to HES records. 245,109 patients had an admission for sepsis in records, after excluding there were a total of 120,374 sepsis cases and 705,959 controls in the initial cohort. Of those 826,333 patients in the initial cohort, there were 526,943 remaining after excluding patients who did not survive their initial sepsis episode (54,568) and controls matched with sepsis cases who died (244,657). Of these there were 71,330 community acquired sepsis cases, 6,064 hospital acquired sepsis cases, 417,010 community controls and 32,539 hospital controls. Figure 1 below shows the exclusion criteria applied to the cohort of cases and controls after hospital discharge. Figure S6.8 in the supplementary materials shows the full inclusion/exclusion flow for the initial cohort.

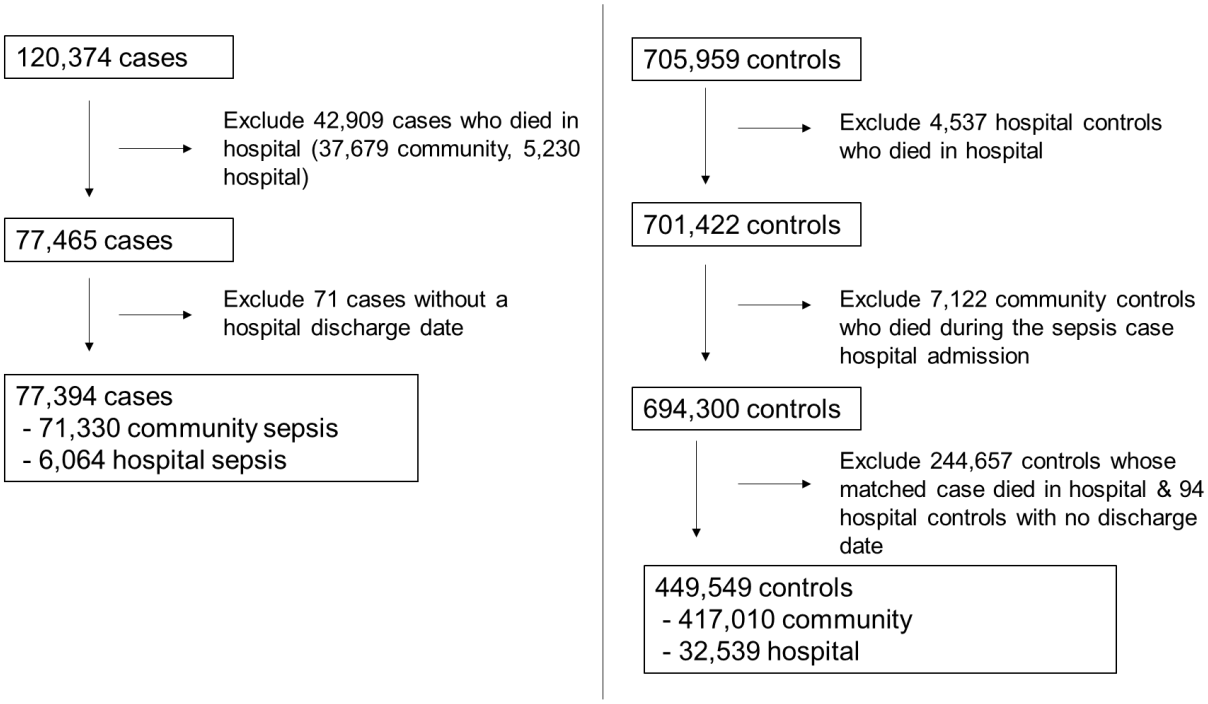


Figure 6.1 *Exclusion criteria for patients.*

Table 1 shows the baseline characteristics of all patients in the cohorts. Around 49% of community patients were female, compared with around 48% in the hospital patient group. The median age was 80 (IQR 73-86) in the community group and 80 (IQR 74-86) in the hospital group. There was no big difference in the median BMI between the community and hospital patients, and only small differences in smoking status. In terms of deprivation there was a slightly higher proportion of cases than controls in the most deprived quintile, particularly in the hospital sepsis group (cases 20.0% vs controls 16.8%).

The median Charlson comorbidity score in the community case group was 2 (IQR 1-4), but in the community control group it was 1 (IQR 0-3), and for the hospital patients the median was 3 (IQR 1-4) for the cases and 2 (IQR 1-4) for the controls. There was a much higher proportion of patients in the community control group with a comorbidity score of 0 compared with any of the other groups. Looking at the individual comorbidities in the community patients there is in general a higher incidence in the case group compared with the controls, with hypertension (58.9%), renal disease (30.7%), cancer (27.6%) and diabetes (26.1%) the most frequently observed comorbidities in the case group. For the hospital group of patients, however, the incidence of comorbidities is more comparable between the cases and controls, with higher proportions of controls having some of the comorbidities including cancer (controls 30.0% vs cases 26.1%), COPD (controls 18.6% vs cases 17.0%) and coronary heart disease (CHD, controls 30.5% vs 26.5%).

All patients, n = 526,943		Community Cohort		Hospital Cohort	
Variable		**Cases (n = 71,330)**	**Controls (n = 417,010)**	**Cases (n = 6,064)**	**Controls (n = 32,539)**
Gender, n female (%)		35,238 (49.4%)	206,141 (49.4%)	2,929 (48.3%)	15,863 (48.8%)
Ethnicity, n (%)	White	61,493 (95.0%)	331,231 (94.8%)	5,200 (94.6%)	28,086 (95.4%)
	Black	1,017 (1.6%)	5,989 (1.7%)	117 (2.1%)	460 (1.6%)
	Asian	1,660 (2.6%)	8,794 (2.5%)	139 (2.5%)	657 (2.2%)
	Other	546 (0.8%)	3,523 (1.0%)	42 (0.8%)	222 (0.8%)
	Missing	6,614	67,473	566	3,114
Age (years), median (IQR)		80 (73, 86)	80 (73, 86)	80 (74, 86)	80 (74, 86)
	60-74	21,285 (29.8%)	124,214 (29.8%)	1,721 (28.4%)	9,217 (28.3%)
	75-84	27,950 (39.2%)	164,595 (39.5%)	2,488 (41.0%)	13,322 (40.9%)
	85-94	19,633 (27.5%)	114,823 (27.5%)	1,658 (27.3%)	8,907 (27.4%)
	>95	2,462 (3.5%)	13,378 (3.2%)	197 (3.2%)	1,093 (3.4%)
BMI (kg/m^2), median (IQR)		27.0 (23.6, 30.6)	26.7 (23.6, 29.6)	27.0 (23.3, 30.1)	26.9 (23.4, 29.9)
	Low BMI (<18.5), n (%)	1,351 (3.6%)	5,528 (2.6%)	114 (3.8%)	591 (3.6%)
	Normal BMI (18.5-24), n (%)	11,441 (30.3%)	70,187 (33.1%)	939 (31.3%)	5,287 (32.1%)
	Overweight (25-30), n (%)	14,210 (37.7%)	87,623 (41.3%)	1,183 (39.4%)	6,569 (39.8%)
	Obese (>30), n (%)	10,696 (28.4%)	48,850 (23.0%)	767 (25.5%)	4,043 (24.5%)
	Missing, n	33,632	204,822	3,061	16,049
Smoking status, n (%)	Current	21,432 (47.7%)	117,077 (47.5%)	1,905 (50.3%)	9,988 (48.5%)
	Ex-smoker (1)	10,183 (22.7%)	52,607 (21.3%)	827 (21.8%)	4,621 (22.4%)
	Non-smoker (0)	13,284 (29.6%)	77,011 (31.2%)	1,058 (27.9%)	5,975 (29.0%)
	Missing	26,431	170,315	2,274	11,955
IMD Quintile, n (%)	1 (least deprived)	15,746 (22.1%)	100,318 (24.4%)	1,253 (20.7%)	7,364 (22.7%)
	2	15,302 (21.5%)	91,409 (22.2%)	1,271 (21.0%)	7,017 (21.6%)
	3	14,236 (20.0%)	81,647 (19.8%)	1,191 (19.7%)	6,828 (21.0%)
	4	13,401 (18.8%)	73,479 (17.9%)	1,158 (19.1%)	5,991 (18.4%)
	5 (most deprived)	12,543 (17.6%)	64,652 (15.7%)	1,179 (19.5%)	5,288 (16.3%)
	Missing	102	5,505	12	51
Charlson comorbidity score, median (IQR)		2.00 (1.00, 4.00)	1.00 (0.00, 3.00)	3.00 (1.00, 4.00)	2.00 (1.00, 4.00)
	0	11,319 (15.9%)	137,246 (32.9%)	919 (15.2%)	4,879 (15.0%)
	1-2	25,111 (35.2%)	150,300 (36.0%)	2,074 (34.2%)	11,664 (35.8%)
	3-4	19,627 (27.5%)	85,494 (20.5%)	1,727 (28.5%)	9,008 (27.7%)
	5-6	9,664 (13.5%)	31,713 (7.6%)	862 (14.2%)	4,314 (13.3%)
	>7	5,609 (7.9%)	12,257 (2.9%)	482 (7.9%)	2,674 (8.2%)
Comorbidity, n (%)	Cancer	19,702 (27.6%)	73,456 (17.6%)	1,582 (26.1%)	9,754 (30.0%)
	Cerebrovascular Disease	13,865 (19.4%)	54,805 (13.1%)	1,355 (22.3%)	6,693 (20.6%)
	COPD	12,315 (17.3%)	57,954 (13.9%)	1,032 (17.0%)	6,037 (18.6%)
	Heart Failure	9,415 (13.2%)	31,998 (7.7%)	941 (15.5%)	4,836 (14.9%)
	Dementia	8,807 (12.3%)	31,059 (7.4%)	634 (10.5%)	2,630 (8.1%)
	Diabetes	18,624 (26.1%)	69,532 (16.7%)	1,669 (27.5%)	7,390 (22.7%)
	HIV	4 (0.0%)	82 (0.0%)	1 (0.0%)	2 (0.0%)
	Liver Disease	778 (1.1%)	1,696 (0.4%)	85 (1.4%)	349 (1.1%)
	Renal Disease	21,876 (30.7%)	97,042 (23.3%)	1,948 (32.1%)	9,921 (30.5%)
	Peripheral Vascular Disease	6,609 (9.3%)	24,975 (6.0%)	603 (9.9%)	3,305 (10.2%)
	Autoimmnune Disease	7,883 (11.1%)	30,242 (7.3%)	690 (11.4%)	3,344 (10.3%)
	Deep Vein Thrombosis	821 (1.2%)	3,256 (0.8%)	67 (1.1%)	336 (1.0%)
	Skin Ulcer	8,628 (12.1%)	23,711 (5.7%)	753 (12.4%)	3,055 (9.4%)
	Coronary Heart Disease	17,389 (24.4%)	80,628 (19.3%)	1,608 (26.5%)	9,933 (30.5%)
	Hypertension	41,995 (58.9%)	225,886 (54.2%)	3,676 (60.6%)	19,353 (59.5%)

Table 6.1. *Baseline demographics for cohort patients*

6.4.2 Mortality (all-cause)

Using cumulative incidence analysis and censoring patients if they came to the end of their CPRD observation period the overall mortality rate after 1 year was 35.2% (95% CI 34.8-35.5%) for community cases, 12.6% (95% CI 12.5-12.7%) for community controls, 46.0% (95% CI 44.7-47.3%) for hospital cases and 28.6% (95% CI 28.1-29.1%) for hospital controls (see Table 2 and Figure S6.1). By the 3-year time point the mortality rates were 57.9% (95% CI 57.5-58.3%) for community cases, 33.2% (95% CI 33.0-33.3%) for community controls,

67.2% (95% CI 65.8-68.4%) for hospital cases and 50.8% (95% CI 50.2-51.4%) for hospital controls (see Figure 2).

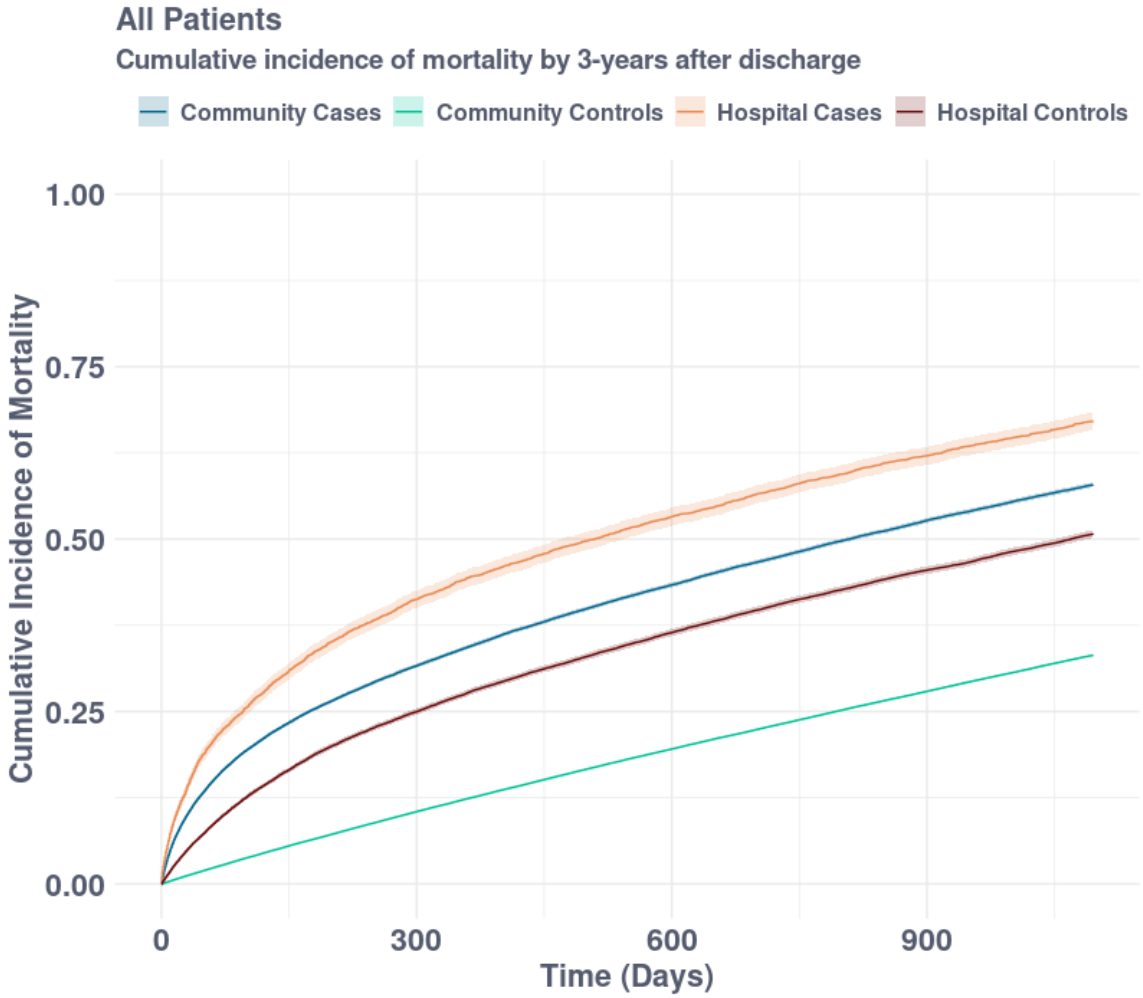


Figure 6.2 *Cumulative incidence plot for 3-year mortality after a sepsis episode by case/control group*

Patients were censored if they had come to the end of their CPRD registration period.

Looking at mortality rates across the demographics (Table S6.1 & Figure S6.2 in supplements), patients in the highest age group in both the community and hospital sepsis groups have the highest mortality rates compared to the lowest age group, Community: 1-year 59.9% (95% CI 57.9-61.9%) vs 26.0% (95% CI 25.4-26.6%), p-value <0.001, Hospital: 1-year 67.7% (95% CI 60.0-74.2%) vs 35.1% (95% CI 32.8-37.5%) . Older control patients also have lower survival rates than controls in the younger age group across both subgroups. There

were only small differences in mortality incidence between patients in terms of either their smoking status or IMD quintile, in all subgroups.

Stratifying by BMI, in both sepsis case groups and control groups, the highest BMI group (>30 kg/m^2) had a lower 1-year mortality rates than patients in the lower BMI groups (community cases 25.5% (95% CI 24.6-26.3%) vs 52.7% (95% CI 49.9-55.4%), hospital cases 41.7% (95% CI 38.0-45.3%) vs 47.1% (95% CI 45.2-48.9%), community controls 6.95% (95% CI 6.73-7.19%) vs 28.7% (95% CI 27.5-29.9%), hospital controls 19.0% (95% CI 17.8-20.2%) vs 45.9% (95% CI 41.6-50.0%)).

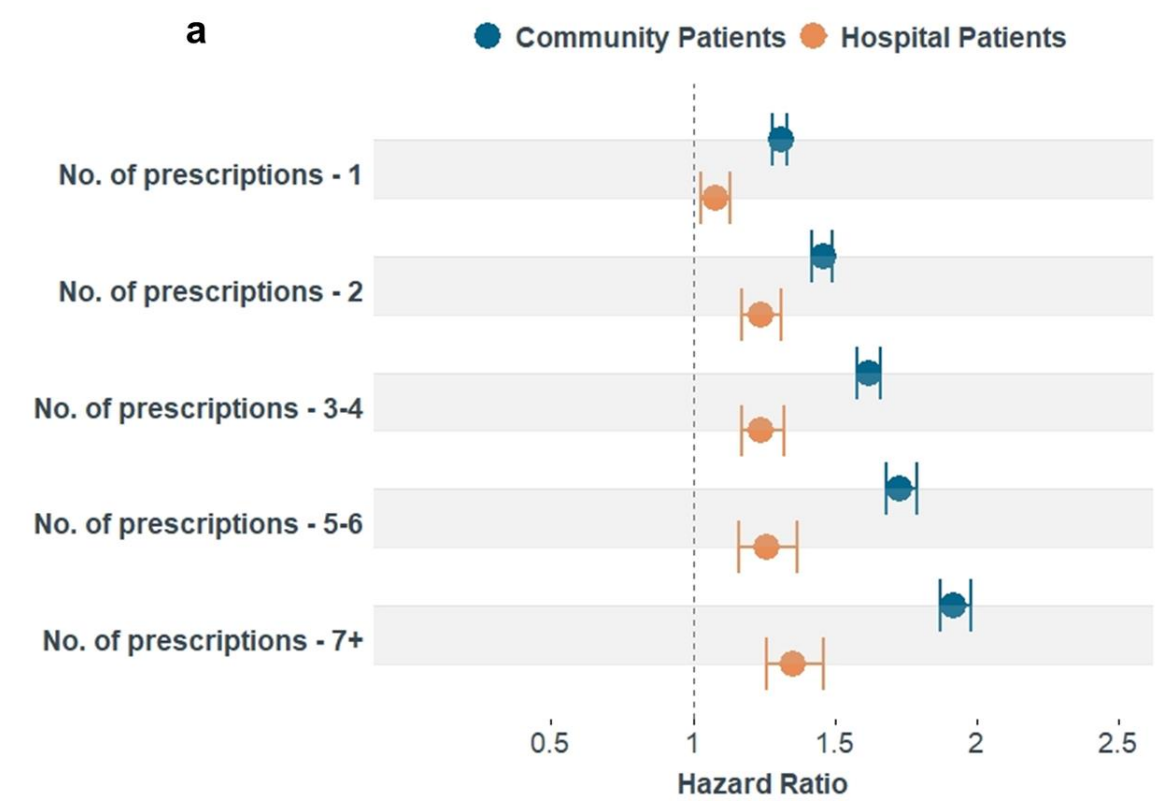
In terms of overall levels of comorbidity, patients in the community sepsis group with a Charlson score of over 7 had higher chance of death at 1-year than patients in either the Charlson score 0 or 1-2 groups (51.5% (95% CI 50.2-52.9%) vs 24.7% (95% CI 23.9%-25.5%) and 33.4% (95% CI 32.8-34.0%), respectively). In the hospital sepsis group, the patients with greater levels of comorbidity did still have higher mortality rates than those with a Charlson score of 0, but the difference was not as large (Charlson score 7+ 56.4% (95% CI 51.7-60.8%) vs Charlson score 0 36.8% (95% CI 33.5-40.1%)).

The patients were also stratified by their antibiotic use in the year prior to initial index date (ie prior to their sepsis hospital admission). Patients in the community sepsis group who had received 0 antibiotic prescriptions had a lower mortality rate at 1 year than patients who were in the highest antibiotic user group (>7, 41.0% (95% CI 39.8-42.3%) vs 30.6% (95% CI 30.0-31.1%)), as did patients with 0 prescriptions in the hospital case group compared with those in the >7 group (42.8% (95% CI 40.7-44.7%) vs 51.3% (95% CI 46.2-56.1%)). For the community control groups there was a much bigger difference in mortality (0 prescriptions 9.26% (95% CI 9.14-9.37%) vs >7 prescriptions 27.7% (95% CI 27.0-28.5%)), whereas the differences in the hospital control groups were smaller (0 prescriptions 25.3% (95% CI 24.5-26.0%) vs 5-6 prescriptions 34.0% (95% CI 31.6-36.4%)).

Figure 6.3 shows the fully adjusted hazard ratios from the Cox proportional hazard model, with 1-year mortality as the outcome, stratifying by the different cohorts (Gold and Aurum). For full results including p-values please see Tables S6.4 (community patients) and S6.5 (hospital patients).

Sepsis cases had significantly higher risk of mortality in both community and hospital patient groups, with HRs of 3.41 (95% CI 3.36-3.47, p<0.001) and 1.91 (95% CI 1.83-2.00, p-value <0.001), respectively. Compared to males, females had a lower risk of death in both cohorts (community HR 0.82, 95% CI 0.81-0.83, p-value <0.001, hospital HR 0.73, 95% CI 0.70-0.76, p-value <0.001). Patients with a BMI <18.5 kg/m^2 had an increased risk of death than those with a BMI of between 18.5 and 24 (community HR 1.86, 95% CI 1.78-1.95, p<0.001, hospital

HR 1.68, 95% CI 1.49-1.90, p<0.001) but those with a higher BMI had a lower risk of death (BMI >30 kg/m^2 community HR 0.64, 95% CI 0.62-0.66, p-value 0.001, hospital HR 0.71, 95% CI 0.66,0.76, p-value <0.001). In terms of comorbidity levels, across both cohorts, patients with a higher Charlson score have a higher risk of death compared to patients with a Charlson score of 0 (community Charlson score >7 HR 3.60, 95% CI 3.49-3.72, p-value <0.001, hospital Charlson score >7 HR 2.41, 95% CI 2.22-2.61, p-value <0.001). Looking at antibiotic prescribing prior to the sepsis episode, patients who had received more antibiotics were at a higher risk of death compared to patients who had not received any antibiotics (community antibiotic group >7 HR 1.92, 95% CI 1.87-1.98, p-value <0.001, hospital antibiotic group >7 HR 1.35, 95% CI 1.26-1.46, p-value <0.001).



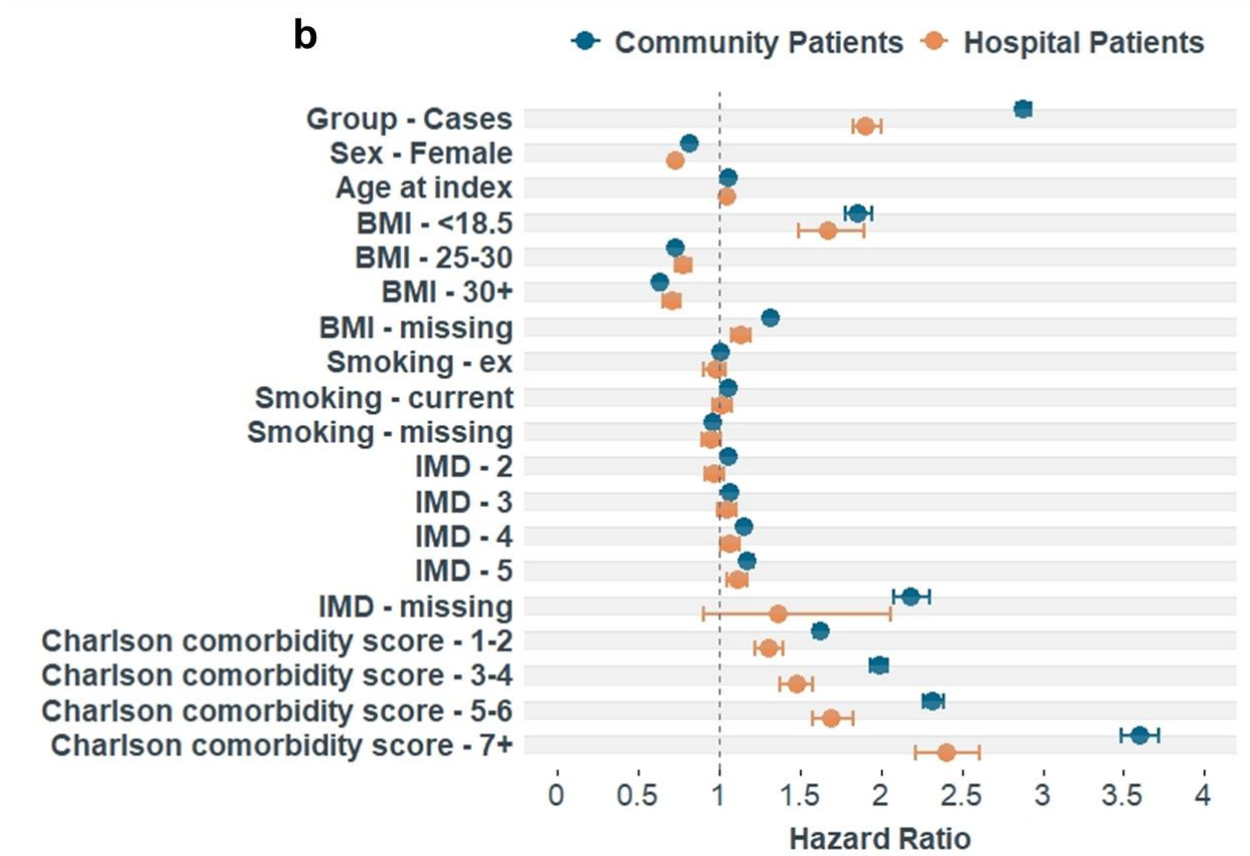


Figure 6.3 *Fully adjusted hazard ratios and 95% confidence intervals from Cox proportional hazard model for 1-year mortality*

p-values are presented in Table S6.4 and S6.5. 6.4a shows prior antibiotic use and 6.4b shows other demographic and comorbidity variables. Reference values for categorical variables as follows: antibiotic prescribing group – 0, group – controls, sex – male, BMI – 18.5-24.5 kg/m^2, smoking – non, IMD – quintile 1 (least deprived), Charlson comorbidity score – 0.

6.4.3 Hospital Readmission (all-cause)

In terms of readmissions to hospital the rates were more similar between the community and hospital sepsis cases, with the incidence of being readmitted within 1 year of 69.1% (95% CI 68.7-69.4%) for the community cases and 68.7% for hospital cases (95% CI 67.5-69.9%) (Table 2, see Table S6.2 for breakdown by demographics/comorbidities). For the control patients, the incidence of readmission was 36.9% for the community controls (95% CI 36.7-37.0%) but much higher for the hospital controls, at 80.1% (95% CI 79.7-80.6%). The all-cause hospital readmission rates at 3-years were 81.2% (95% CI 80.9-81.5%), 77.9% (95% CI 76.8-79.0%), 64.2% (95% CI 64.0-64.3%, and 88.4% (95% CI 88.0-88.7%) for community sepsis cases, hospital sepsis cases, community controls and hospital controls, respectively.

The results from the multivariable Fine-Grey competing risks model with readmission as the outcome and death as the competing risk are displayed in Tables S6.6 and S6.7. In the community group cases had a significantly increased risk of hospital readmission with an adjusted HR of 2.50 (95% CI 2.47-2.53). However, in the hospital group the cases had a lower risk of readmission compared to the controls, with a HR of 0.68 (95% CI 0.66-0.70). In both groups increased Charlson comorbidity score and antibiotic prescriptions increased the risk of readmission.

	Community Sepsis		Hospital Sepsis	
	Cases (n = 71,330)	**Controls (n = 417,010)**	**Cases (n = 6,064)**	**Controls (n = 32,539)**
Cumulative incidence - mortality				
All cause 1-year	35.2% (34.8%, 35.5%)	12.6% (12.5%, 12.7%)	46.0% (44.7%, 47.3%)	28.6% (28.1%, 29.1%)
All cause 3-year	57.9% (57.5%, 58.3%)	33.2% (33.0%, 33.3%)	67.2% (65.8%, 68.4%)	50.8% (50.2%, 51.4%)
Cumulative incidence - hospital readmission				
All cause 1-year	69.1% (68.7%, 69.4%)	36.9% (36.7%, 37.0%)	68.7% (67.5%, 69.9%)	80.1% (79.7%, 80.6%)
All cause 3-year	81.2% (80.9%, 81.5%)	64.2% (64.0%, 64.3%)	77.9% (76.8%, 79.0%)	88.4% (88.0%, 88.7%)

Table 6.2 *Cumulative incidence for mortality and hospital readmission*

Patients were censored if they had come to the end of their CPRD registration period. For the hospital readmission outcome death was adjusted for as a competing risk.

6.4.4 Incidence of GP common infection consultations and antibiotic prescriptions

There were 544,383 GP consults for common infections in the year following index, and 1,149,845 in the 3-year period. The most frequent indication for a consult for the sepsis cases was a urinary tract infection (UTI) for the community cases (1-year 22.5%, 3-year 22.1% of infection consults) and the hospital cases (1-year 22.8% and 3-year 21.9% of infection consults). In the year prior to index the most frequently observed infection for the community cases was also UTI (20.8%) but for the hospital cases it was a skin indication (19.2%). For both groups of control patients, the most common infection in the pre- and post- sepsis periods was an infection related to asthma or COPD. There were 9,394 occurrences of a GP record of sepsis (7.7% of consults) in the community case group compared with 1,363 (0.4%) in the control group for the first year after index (3-year cases 4.9% vs controls 0.4%), and for the hospital group there were 501 (6.0%) in the case group and 0 in the control group (3-year cases 656, 4.2%, vs controls 0).

The proportion of community sepsis cases having an infection in the 1-year follow up period was 52.3%, higher than for the community control group at 34.2% (3-year cases 61.2% vs

controls 49.4%). However, for the hospital patients the proportion of controls and cases with an infection consult was 43.5% (3-year cases 51.1% vs controls 55.9%).

There were 681,692 prescriptions for an antibiotic within the first year of follow-up and 1,464,371 within 3 years. The most frequently prescribed antibiotics across the subgroups of patients were amoxicillin, trimethoprim, flucloxacillin, nitrofurantoin and doxycycline, which were the most common ones in the period prior to sepsis. There were 38,938 community cases (54.6%) receiving a prescription in the first year, compared with 157,435 (37.8%) community controls. For hospital patients there were 2,829 cases (46.7%) and 16,447 (50.5%) controls receiving prescriptions in the first year. Comparing to the year prior to sepsis there was an increase in the proportion of patients in all groups who had no antibiotic prescriptions, however this did not take into account patients who are lost to follow-up in the post-sepsis period.

Using Kaplan-Meier analysis to censor patients who have either died or been lost to follow-up the, the probability of not receiving an antibiotic after 1 year after index was 32.5% (95% Ci 32.1-32.9%) in the community case group, compared with 59.5% (95% CI 59.3-59.6%) in the community control group (p-value <0.001), 34.7% (95% CI 33.1-36.2%) in the hospital case group and 40.4% (95% CI 39.8-41.0%) in the hospital control group (p-value <0.001). By the end of the 3-year follow-up period the probability was 15.7% (95% CI 15.3-16.1%) and 17.7% (95% CI 16.2-19.3%) for the community cases and hospital cases, respectively (see Figure S6.3).

Across the case and control groups the Charlson comorbidity score at index and the number of antibiotics in the year prior to sepsis did have an effect on the probability of receiving an antibiotic. In the community case group patients with the highest Charlson comorbidity score had a lower probability than those with a Charlson score of 0 (24.4% (95% CI 23.0-25.9%) vs 43.2% (95% CI 42.2-44.2%), p-value <0.001) and for the hospital cases it was 31.1% (95% CI 25.8-37.4%) vs 44.4% (95% CI 40.6-48.5%, p-value <0.001). In terms of prior antibiotic use patients in the highest antibiotic user group (7+ prescriptions) had a very low probability of not receiving an antibiotic in the year following year across all patient groups (community cases 5.6% (95% CI 4.9-6.4%), community controls 5.2% (95% CI 4.8-5.6%), hospital cases 7.8% (95% CI 4.6-13.1%) and hospital controls 6.0% (95% CI 4.8-7.4%)).

For the other demographic factors, the results were more mixed. In terms of age there was a bigger difference in the oldest vs youngest control patient groups than for the cases. In the community cases the probability of not receiving an antibiotic for patients >95 was 27.5% (95% CI 25.1-30.1%), compared with 34.8% (95% CI 24.1-35.6%) for patients in the 60-74 age group (p-value <0.001). However, for the community controls the probability was 42.8% (95%

CI 41.9-43.8%) in the highest age group and 67.7% (95% CI 67.4-68.0%) in the lower age group (p-value <001). The effects of smoking, BMI and deprivation score did vary (see Table S6.3).

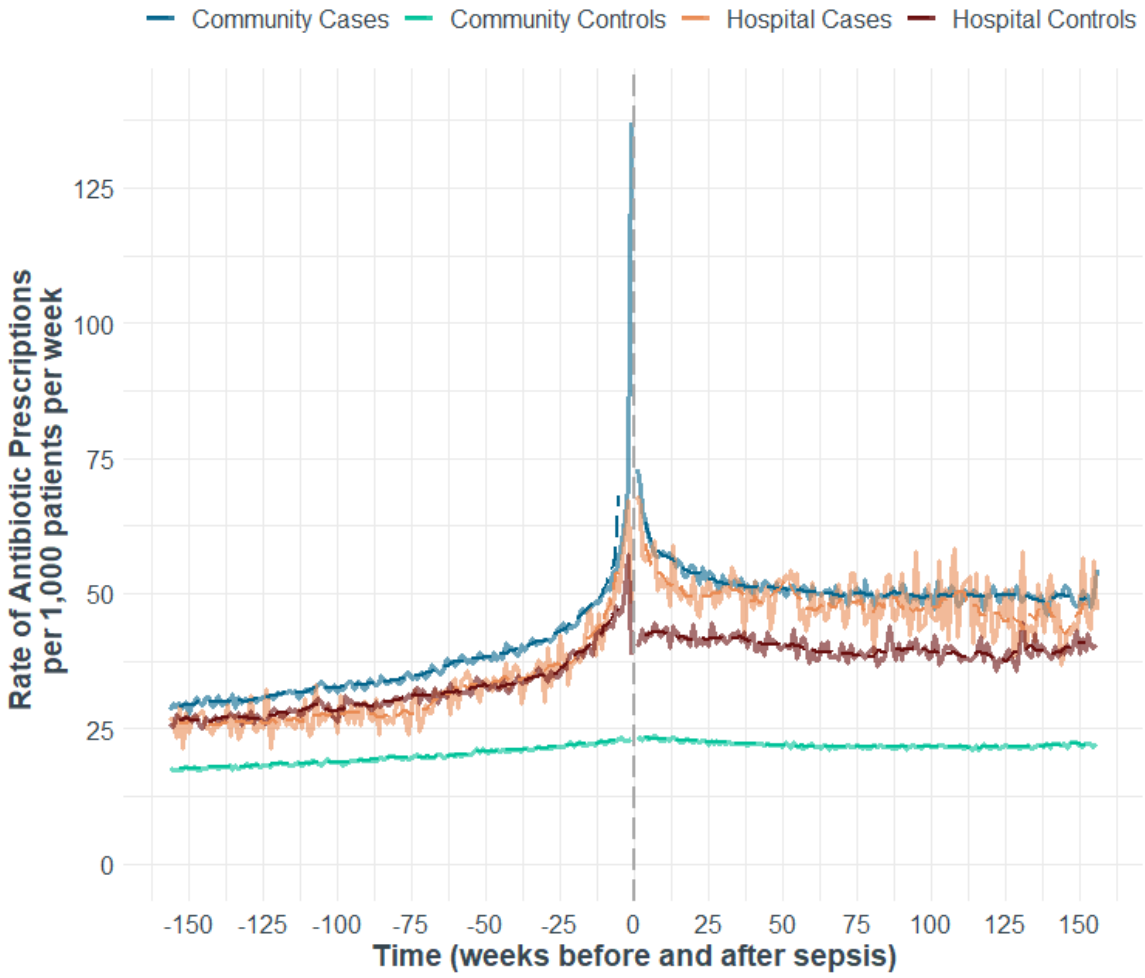


Figure 6.4. *Antibiotic prescribing rates for the 3-year period pre- and post- sepsis*

Rates have been calculated per 1,000 people per week, to account for patients who have died or lost to follow up. The dashed grey line shows the sepsis episode.

For the community controls (green line), the rates of both infections (Figure S6.5) and prescriptions (Figure 6.4) stayed roughly the same, although there was a slight gradual increase over the 6 years. The community cases group (blue line) started to see an increase within around 25 weeks of their sepsis admission and reaches a high level just before sepsis, and whilst it did decrease again following discharge from hospital it remained consistently higher in the post sepsis 3-year period. Both the hospital cases (orange line) and hospital controls (red line) also see an increase in the time immediately prior to sepsis, although not

as high as for the community cases. After sepsis the hospital case rates did reduce, but similarly to the community cases it did not return to the same level as before sepsis. For the hospital control patients their rates reduced more quickly following discharge but were higher than they were before their hospital admissions. Overall, rates of antibiotic prescribing were higher than rates of common infection.

Comorbidity score

Across the patient groups there was an increase in comorbidity levels following a sepsis episode. Within the first year 19.9% of community cases saw an increase in their Charlson comorbidity score compared to 11.3% in the controls. In the hospital cohort 22.2% of cases saw an increase in score compared with 19.3% of controls. For patients who were still alive and still registered in CPRD between 1 and 3 years after sepsis the proportion of community cases who had an increase in Charlson comorbidity score was 36.1% compared to 23.6% for the controls. The proportion of hospital cases was higher than the community cases, at 41.0%, and the hospital control group was 34.7%.

6.5 Discussion

6.5.1 Key findings

This study found that patients who survived an initial sepsis hospital admission were at risk of long-term mortality and hospital readmission. Those who contracted sepsis in the hospital had higher mortality and hospital readmission rates than those in the community. Higher levels of comorbidity and antibiotic use prior to a sepsis episode also increased the risk of death and readmission, however, these effects differed in the subgroups of patients with community-acquired and hospital-acquired sepsis. The incidence of antibiotic use and consults for common infections increased for both groups of sepsis patients in the three year period after sepsis.

6.5.2 How do the findings fit in with the existing literature?

The mortality rates in our study are high compared to some other studies. A systematic review and meta-analysis conducted by Shankar-Hari et al[12] reported a mean 1-year mortality rate of 16.1%, although there was a lot of variation depending on how the patients had been identified and the severity of sepsis. As we looked at an older group of patients this may be why mortality was high. Weycker et al[13] stratified severe sepsis by age group and reported 1-year mortality rates for 65-84 as 52.1%, and 85+ as 64.7%, which are higher than in our study.

There are a few studies looking at the factors affecting long-term mortality. A 2019 study by Shankar-Hari et al used UK ICNARC data and used a combination of pre-existing comorbidity levels and severity of illness/type of infections to predict mortality. They found that patients with two or more severe comorbidities had significantly worse survival than those with none. However they only included patients who had been admitted to ICU, and the comorbidity information came from data captured during their hospital stay, not from their primary care records[3].

The study by Prescott et al[2], using data from a US cohort study, was one of few studies to include a propensity-score matched control groups within their study and included a combination of sepsis-specific and pre-sepsis health predictors to predict mortality. They concluded that the late mortality in sepsis patients could not be attributed to age, sociodemographic factors or pre-existing conditions when compared with hospital admissions for non-sepsis or patients who had not been in hospital. The study did not, however, look to see if there were differences between hospital- and community- acquired sepsis patients.

In this study both 1-year and 3-year mortality rates were significantly higher in the hospital-acquired sepsis group compared to community-acquired sepsis patients. Prior antibiotic use and comorbidity levels increased the risk of mortality and hospital readmission following sepsis in both community-acquired and hospital-acquired sepsis, however the effects were reduced in the hospital-acquired sepsis group. Hospital-acquired sepsis patients tend to have more severe illness, with longer lengths of stay, higher levels of organ dysfunction and in-hospital mortality[14–16]. It might be factors relating to their acute sepsis episode that impact risk of late mortality. This adds further evidence that there are aetiological differences between the two patient groups. Interestingly, the rates of antibiotic prescribing are similar in the 3-year period after sepsis for community- and hospital- acquired sepsis patients, which may indicate that prolonged immune system impairment[17] and gut microbiota disruption[6] is similar in both patient groups.

In terms of readmission there are many papers assessing short-term (30- days) readmissions, but few looking at longer term. Liu et al[8] reported a 1-year readmission rate of 48% in patients in the US, Prescott et al[18] found a 63% 1-year admission rate in survivors of severe sepsis, and Yende et al reported a rate of 43% in a multi-centre US study[19]. These were all lower than in this study, where the 1-year readmission cumulative incidence rates were 69.1% and 68.7% for the community and hospital sepsis cases, respectively. This may be due to the age restriction in our study as older people may be at higher risk of hospital admission. The mean age of patients in the study by Yende et al[20] was 60.5 years and in the study by Liu et al[8] they reported that 28.9% of their study population were younger than 65. Prescott et al[18] did report

a mean age in their cohort of 78.5 years, slightly lower than in our cohort. All three studies found similar characteristics associated with increased risk of admissions, with older age and increased comorbidity scores.

The levels of comorbidity in the case and control groups both increased compared to the pre-sepsis period, however the increase was more substantial in the case groups compared to the controls. As patients age they are at greater risk of developing comorbidities, especially in a population over the age of 65. The fact that there was an increase in Charlson score in a higher proportion of cases than controls suggests that sepsis does have some effect. The increased burden of patients suffering with more chronic conditions e.g. cardiovascular disease, kidney disease as well as cognitive impairment has been found in other studies[6,21].

Studies looking at use of healthcare services in sepsis survivors mainly focus on hospital care or community care services such as nurse visits or residence in a care facility. There are no studies looking at use of primary care services, consultations for common infection or use of antibiotics following a sepsis episode. There are a few studies looking at the prolonged impairment of the immune system following sepsis[17,22], and a study by Yende et al[19] found that levels of inflammatory and immunosuppression biomarkers remain increased for up to a year in some patients. Additionally, the majority of sepsis patients will have been treated with antibiotics during their sepsis episode and antibiotics are known to be disruptors of the gut microbiota[6]. This combination of factors could be why in this study the levels of antibiotic use and infection prevalence were higher in the post-sepsis period.

6.5.3 Strengths & Limitations

There are several strengths of this study. We accessed a large, national database of both primary and secondary care electronic health record data. This meant we could identify patients with sepsis in hospital admissions data and follow them up with their primary care records. We were also able to identify separate control groups for patients who developed sepsis in the community or hospital, which is the first study we're aware of to do so.

With access to patient's primary care records and death data from ONS we were able to follow patients up for a long period of time, up to a maximum of 3 years, so we could assess the longer-term burden of sepsis. As well as looking at long-term mortality and hospital readmissions we were also able to look at how use of antibiotics changes following sepsis, and whether they developed additional comorbidities.

There were a few limitations of the study. We used ICD-10 codes to identify sepsis patients, which has been shown to underestimate the number of sepsis patients. Due to the limited

information available in the HES records it was not possible to identify sepsis using clinical observations and the sepsis-3 criteria. Secondly, as we only included patients above the age of 65, to make use of available data, this does limit the generalisability of our results and introduce a potential bias towards patients who have higher comorbidity levels than the general population.

We did not compare sepsis by severity of illness. Although hospital-acquired sepsis cases had a higher in-hospital mortality and longer length of stay than community-acquired sepsis cases, we did not stratify patients by how severe their sepsis was (for example sepsis and septic shock[23]. Due to the limited data available in HES records we could not include information around severity of illness, for example level of organ dysfunction, or type of infection as potential risk factors for mortality or readmission. We also did not have any data around the antibiotics used to treat sepsis, or timings of those antibiotics. These are factors that could also have affected the risk of log-term mortality and readmission.

Another limitation was that not all patients had the same follow-up time, as some patients left their GP or the practices were no longer contributing to CPRD. This meant we had to censor patients if they did not have the full 3-year follow-up period.

6.5.4 Conclusion

The aims of this study were to evaluate the longer-term outcomes of patients who have survived sepsis, in terms of mortality, readmission to hospital and use of primary care. We also aimed to compare these outcomes between patients who developed sepsis in the community and in hospital.

We found that patients who survived an episode of sepsis were not only at higher risk of long-term mortality and hospital readmission but also are at risk of increased use of consultations for common infections and antibiotic use in primary care. This could help inform management of sepsis survivor patients or identify those at greatest risk of mortality and healthcare use.

6.7 References

1. Rudd, K. E. *et al.* Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *The Lancet* **395**, 200–211 (2020).

2. Prescott, H. C., Osterholzer, J. J., Langa, K. M., Angus, D. C. & Iwashyna, T. J. Late mortality after sepsis: propensity matched cohort study. *BMJ* **353**, i2375 (2016).

3. Shankar-Hari, M., Harrison, D. A., Ferrando-Vivas, P., Rubenfeld, G. D. & Rowan, K. Risk Factors at Index Hospitalization Associated With Longer-term Mortality in Adult Sepsis Survivors. *JAMA Netw Open* **2**, e194900 (2019).

4. Shankar-Hari, M. *et al.* Rate and risk factors for rehospitalisation in sepsis survivors: systematic review and meta-analysis. *Intensive Care Med* (2020) doi:10.1007/s00134-019-05908-3.

5. Shankar-Hari, M. & Rubenfeld, G. D. Understanding Long-Term Outcomes Following Sepsis: Implications and Challenges. *Curr Infect Dis Rep* **18**, (2016).

6. Mostel, Z. *et al.* Post-sepsis syndrome- A n evolving entity that afflicts survivors of sepsis. *Molecular Medicine* **26**, 1–14 (2019).

7. Jones, T. K. *et al.* Post–Acute Care Use and Hospital Readmission after Sepsis. *Ann Am Thorac Soc* **12**, 904–913 (2015).

8. Liu, V. *et al.* Hospital readmission and healthcare utilization following sepsis in community settings. *J Hosp Med* **9**, 502–7 (2014).

9. Lee, R. J. *et al.* Determinants of Health-Related Quality of Life After ICU. *Crit Care Med* **46**, 1 (2017).

10. Wolf, A. *et al.* Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. *Int J Epidemiol* **48**, 1740-1740G (2019).

11. Herrett, E. *et al.* Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* **44**, 827–836 (2015).

12. Shankar-Hari, M. *et al.* Evidence for a causal link between sepsis and long-term mortality: A systematic review of epidemiologic studies. *Crit Care* **20**, 1–13 (2016).

13. Weycker, D., Akhras, K. S., Edelsberg, J., Angus, D. C. & Oster, G. Long-term mortality and medical care charges in patients with severe sepsis. *Crit Care Med* **31**, 2316–2323 (2003).

14. Rothman, M. *et al.* Sepsis as 2 problems: Identifying sepsis at admission and predicting onset in the hospital using an electronic medical record–based acuity score. *J Crit Care* **38**, 237–244 (2017).

15. Page, D. B., Donnelly, J. P. & Wang, H. E. Community-, Healthcare-, and Hospital-Acquired Severe Sepsis Hospitalizations in the University HealthSystem Consortium. *Crit Care Med* **43**, 1945–51 (2015).

16. Tonai, M. *et al.* Hospital-onset sepsis and community-onset sepsis in critical care units in Japan: a retrospective cohort study based on a Japanese administrative claims database. *Crit Care* **26**, 1–9 (2022).

17. Moioffer, S. J. *et al.* Severity of Sepsis Determines the Degree of Impairment Observed in Circulatory and Tissue-Resident Memory CD8 T Cell Populations. *The Journal of Immunology* **207**, 1871–1881 (2021).

18. Prescott, H. C., Langa, K. M., Liu, V., Escobar, G. J. & Iwashyna, T. J. Increased 1-Year Healthcare Use in Survivors of Severe Sepsis. *Am J Respir Crit Care Med* **190**, 62–69 (2014).

19. Yende, S. *et al.* Long-term Host Immune Response Trajectories Among Hospitalized Patients With Sepsis. *JAMA Netw Open* **2**, e198686–e198686 (2019).

20. Yende, S. *et al.* Long-term Host Immune Response Trajectories Among Hospitalized Patients With Sepsis. *JAMA Netw Open* **2**, (2019).

21. Yende, S., Iwashyna, T. J. & Angus, D. C. Interplay between sepsis and chronic health. *Trends Mol Med* **20**, 234–238 (2014).

22. He, W. *et al.* Recurrent Sepsis Exacerbates CD4 + T Cell Exhaustion and Decreases Antiviral Immune Responses. *Front Immunol* **12**, (2021).

23. Singer, M. *et al.* The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* **315**, 801 (2016).

6.8 Supplementary materials

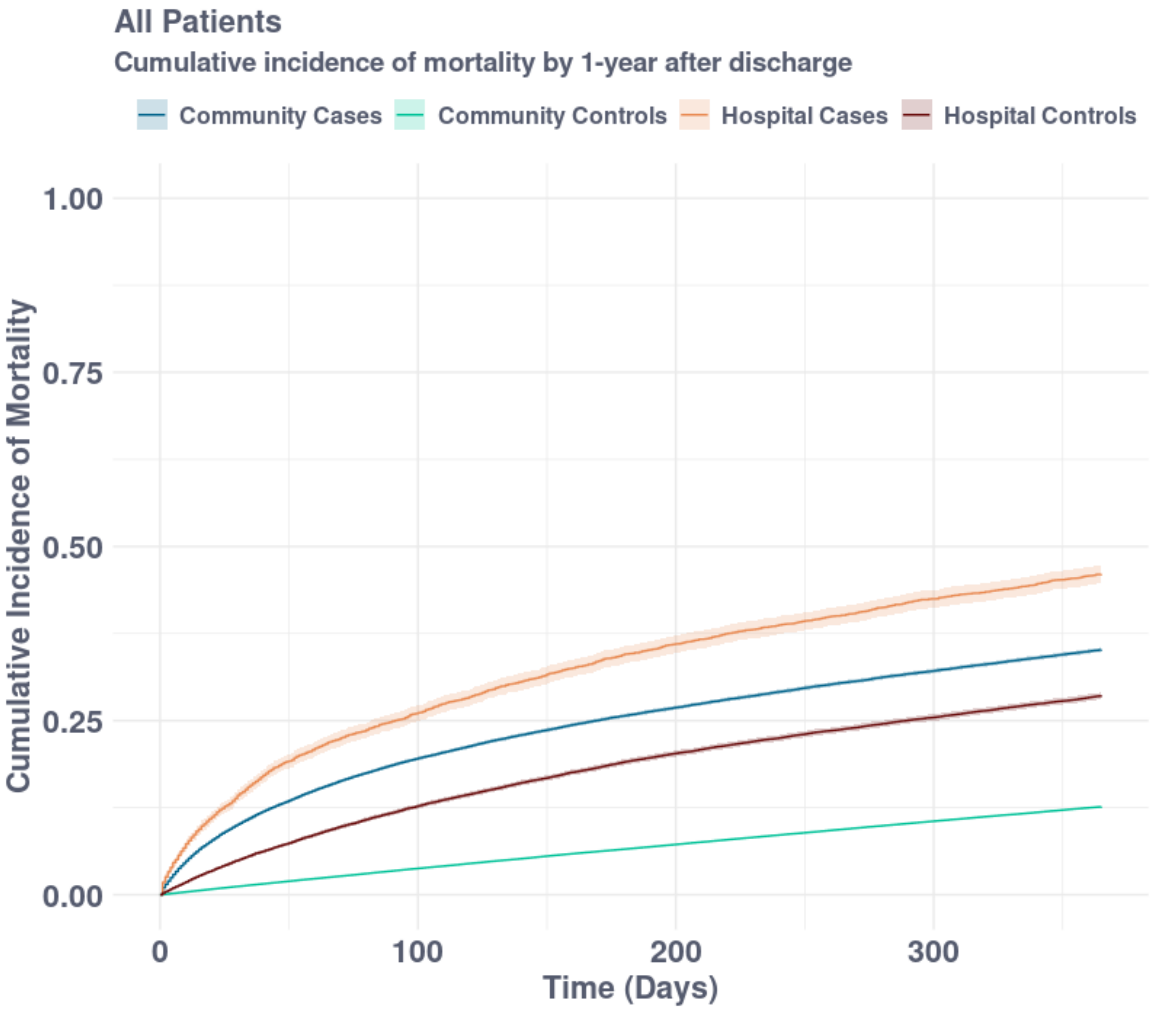
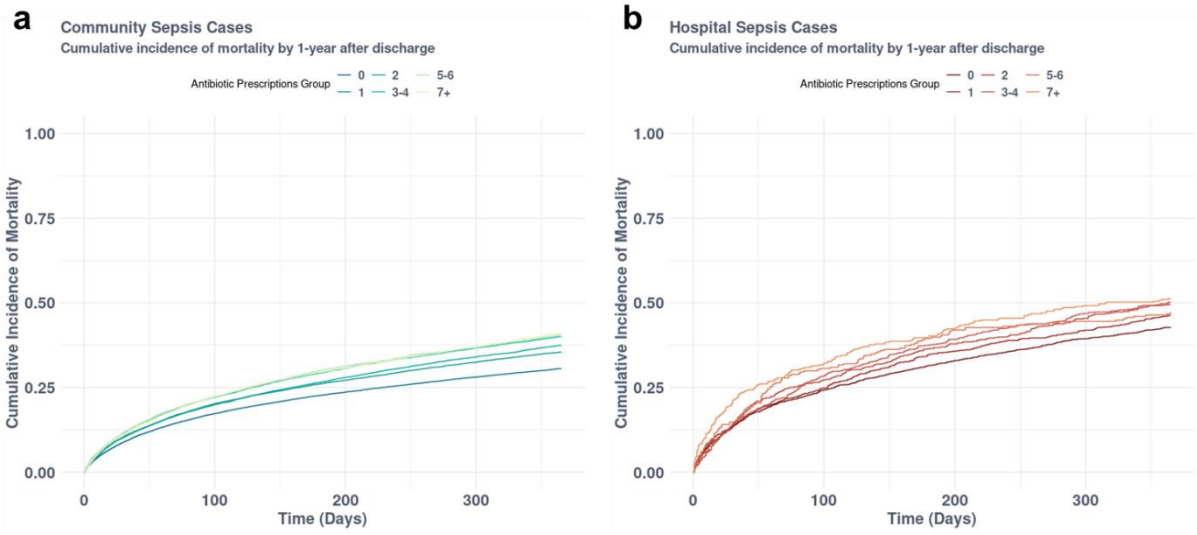
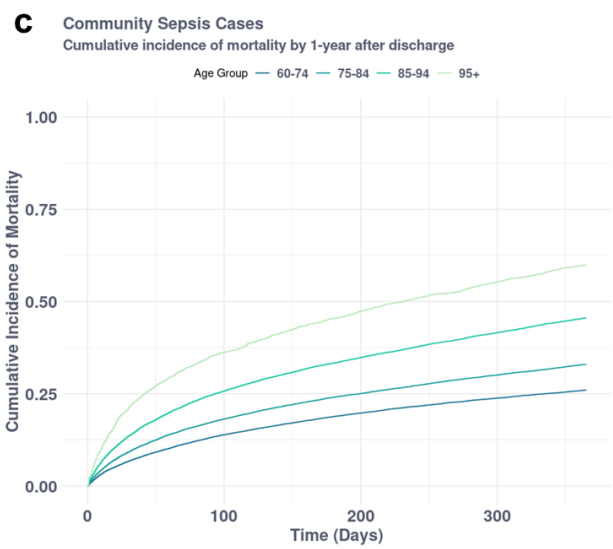


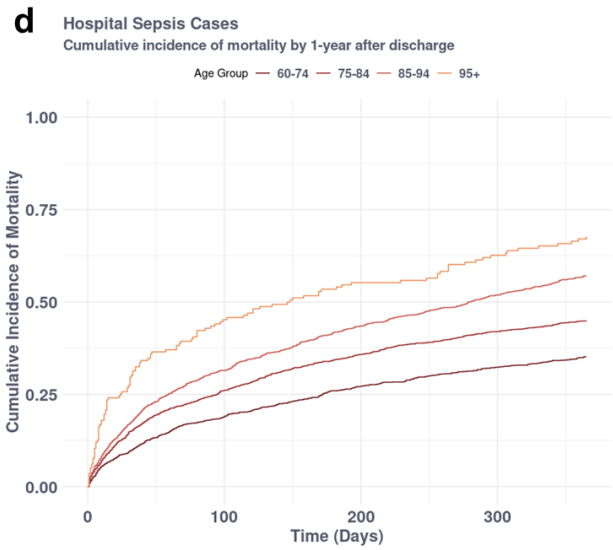
Figure S6.1 *Cumulative incidence plot for 1-year mortality after a sepsis episode by case/control group*

		Cumulative Incidence of Mortality - 1 year			
		Community Sepsis		Hospital Sepsis	
Covariate		Cases (n = 71,330)	Controls (n = 417,010)	Cases (n = 6,064)	Controls (n = 32,539)
Antibiotic Prescriptions Group	0	30.6% (30.0%, 31.1%)	9.26% (9.14%, 9.37%)	42.8% (40.7%, 44.7%)	25.3% (24.5%, 26.0%)
	1	35.5% (34.7%, 36.3%)	14.5% (14.2%, 14.7%)	46.3% (43.4%, 49.1%)	28.1% (27.0%, 29.2%)
	2	37.5% (36.5%, 38.5%)	17.7% (17.2%, 18.1%)	50.2% (46.3%, 53.9%)	32.5% (31.0%, 34.1%)
	3-4	40.1% (39.1%, 41.1%)	21.0% (20.5%, 21.4%)	49.5% (45.7%, 53.2%)	33.1% (31.6%, 34.7%)
	5-6	40.5% (39.0%, 42.0%)	24.2% (23.4%, 25.0%)	47.1% (41.2%, 52.8%)	34.0% (31.6%, 36.4%)
	7+	41.0% (39.8%, 42.3%)	27.7% (27.0%, 28.5%)	51.3% (46.2%, 56.1%)	-
Age Group	60-74	26.0% (25.4%, 26.6%)	4.64% (4.53%, 4.77%)	35.1% (32.8%, 37.5%)	18.6% (17.8%, 19.4%)
	75-84	33.0% (32.4%, 33.6%)	10.8% (10.6%, 10.9%)	44.9% (42.9%, 46.9%)	26.2% (25.4%, 26.9%)
	85-94	45.6% (44.9%, 46.3%)	21.3% (21.0%, 21.5%)	57.1% (54.5%, 59.6%)	39.7% (38.6%, 40.8%)
	>95	59.9% (57.9%, 61.9%)	36.6% (35.8%, 37.5%)	67.7% (60.0%, 74.2%)	58.4% (55.2%, 61.4%)
BMI (kg/m^2)	missing	37.7% (37.2%, 38.2%)	15.3% (15.1%, 15.4%)	47.1% (45.2%, 48.9%)	32.0% (31.3%, 32.7%)
	<18.5	52.7% (49.9%, 55.4%)	28.7% (27.5%, 29.9%)	58.9% (48.7%, 67.7%)	45.9% (41.6%, 50.0%)
	18.5-24	39.8% (38.9%, 40.7%)	13.0% (12.8%, 13.3%)	51.2% (47.8%, 54.6%)	30.1% (28.8%, 31.4%)
	25-30	31.2% (30.5%, 32.0%)	8.41% (8.22%, 8.60%)	40.8% (37.9%, 43.7%)	23.5% (22.5%, 24.6%)
	>30	25.5% (24.6%, 26.3%)	6.95% (6.73%, 7.19%)	41.7% (38.0%, 45.3%)	19.0% (17.8%, 20.2%)
Smoking	missing	35.6% (35.0%, 36.2%)	12.6% (12.5%, 12.8%)	47.9% (45.7%, 50.0%)	28.2% (27.4%, 29.1%)
	0 (never)	36.2% (35.4%, 37.1%)	12.6% (12.4%, 12.8%)	46.3% (43.1%, 49.4%)	29.1% (27.9%, 30.3%)
	1(ex)	35.4% (34.4%, 36.3%)	12.6% (12.3%, 12.9%)	43.1% (39.5%, 46.6%)	28.2% (26.8%, 29.5%)
	2 (current)	34.0% (33.3%, 34.6%)	12.7% (12.5%, 12.9%)	45.0% (42.6%, 47.3%)	28.9% (28.0%, 29.8%)
of Multiple Deprivation	missing	49.8% (39.1%, 59.5%)	35.6% (34.3%, 36.9%)	89.6% (25.0%, 99.1%)	26.6% (15.1%, 39.6%)
	1	34.6% (33.8%, 35.4%)	11.4% (11.2%, 11.6%)	46.0% (43.1%, 48.8%)	28.2% (27.2%, 29.3%)
	2	35.1% (34.3%, 35.8%)	12.2% (12.0%, 12.4%)	45.9% (43.0%, 48.8%)	27.2% (26.2%, 28.3%)
	3	34.7% (33.9%, 35.5%)	12.3% (12.0%, 12.5%)	45.8% (42.9%, 48.8%)	29.1% (28.0%, 30.2%)
	4	36.2% (35.3%, 37.0%)	13.1% (12.8%, 13.3%)	45.6% (42.6%, 48.6%)	29.1% (28.0%, 30.3%)
	5 (most deprived)	35.4% (34.5%, 36.2%)	13.3% (13.0%, 13.6%)	46.3% (43.3%, 49.2%)	-
Charlson comorbidity score	0	24.7% (23.9%, 25.5%)	6.19% (6.06%, 6.32%)	36.8% (33.5%, 40.1%)	18.5% (17.4%, 19.7%)
	1-2	33.4% (32.8%, 34.0%)	12.4% (12.2%, 12.6%)	45.7% (43.5%, 48.0%)	25.5% (24.7%, 26.4%)
	3-4	36.6% (35.9%, 37.3%)	17.5% (17.3%, 17.8%)	44.9% (42.4%, 47.3%)	30.6% (29.6%, 31.6%)
	5-6	39.3% (38.3%, 40.3%)	21.3% (20.8%, 21.8%)	52.5% (49.0%, 55.9%)	34.0% (32.6%, 35.5%)
	7+	51.5% (50.2%, 52.9%)	30.9% (30.1%, 31.7%)	56.4% (51.7%, 60.8%)	44.1% (42.1%, 46.0%)

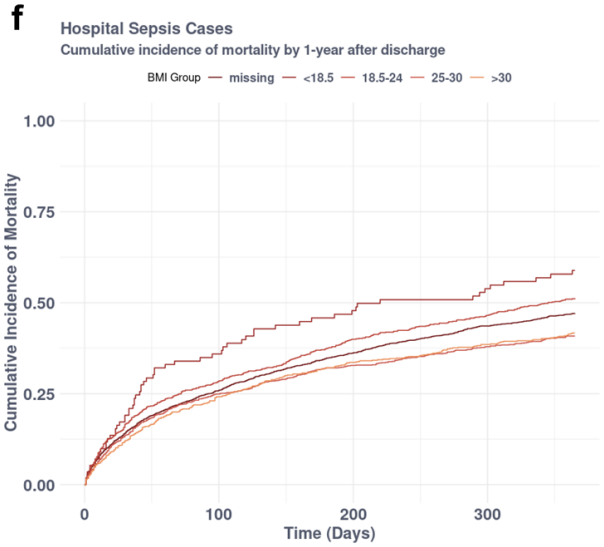
Table S6.1 *Cumulative incidence for 1-year mortality after a sepsis episode*

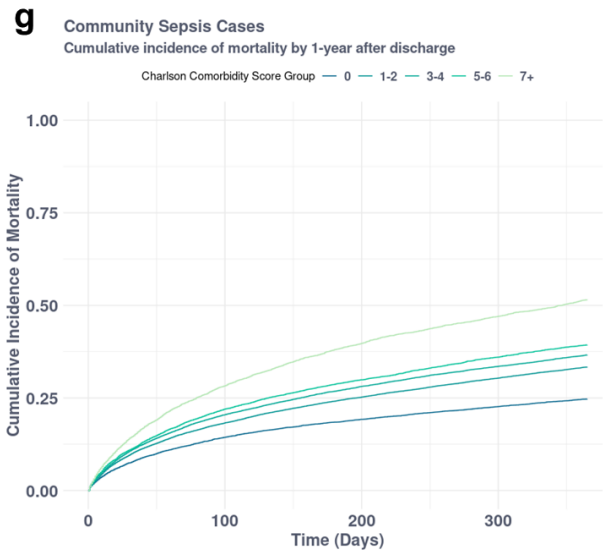


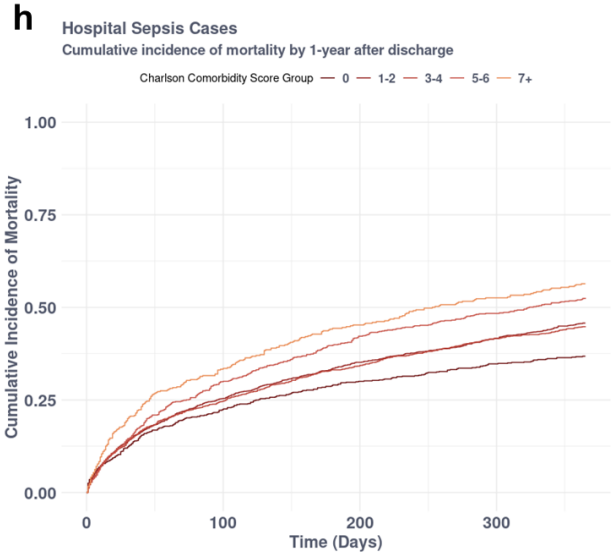

c
Community Sepsis Cases
Cumulative incidence of mortality by 1-year after discharge
Age Group 60-74 75-84 85-94 95+
Cumulative Incidence of Mortality
1.00
0.75
0.50
0.25
0.00
0
100
200
300
Time (Days)


d
Hospital Sepsis Cases
Cumulative incidence of mortality by 1-year after discharge
Age Group 60-74 75-84 85-94 95+
Cumulative Incidence of Mortality
1.00
0.75
0.50
0.25
0.00
0
100
200
300
Time (Days)


e
Community Sepsis Cases
Cumulative incidence of mortality by 1-year after discharge
BMI Group missing <18.5 18.5-24 25-30 >30
Cumulative Incidence of Mortality
1.00
0.75
0.50
0.25
0.00
0
100
200
300
Time (Days)


f
Hospital Sepsis Cases
Cumulative incidence of mortality by 1-year after discharge
BMI Group missing <18.5 18.5-24 25-30 >30
Cumulative Incidence of Mortality
1.00
0.75
0.50
0.25
0.00
0
100
200
300
Time (Days)


g
Community Sepsis Cases
Cumulative incidence of mortality by 1-year after discharge
Charlson Comorbidity Score Group 0 1-2 3-4 5-6 7+
Cumulative Incidence of Mortality
1.00
0.75
0.50
0.25
0.00
0
100
200
300
Time (Days)


h
Hospital Sepsis Cases
Cumulative incidence of mortality by 1-year after discharge
Charlson Comorbidity Score Group 0 1-2 3-4 5-6 7+
Cumulative Incidence of Mortality
1.00
0.75
0.50
0.25
0.00
0
100
200
300
Time (Days)

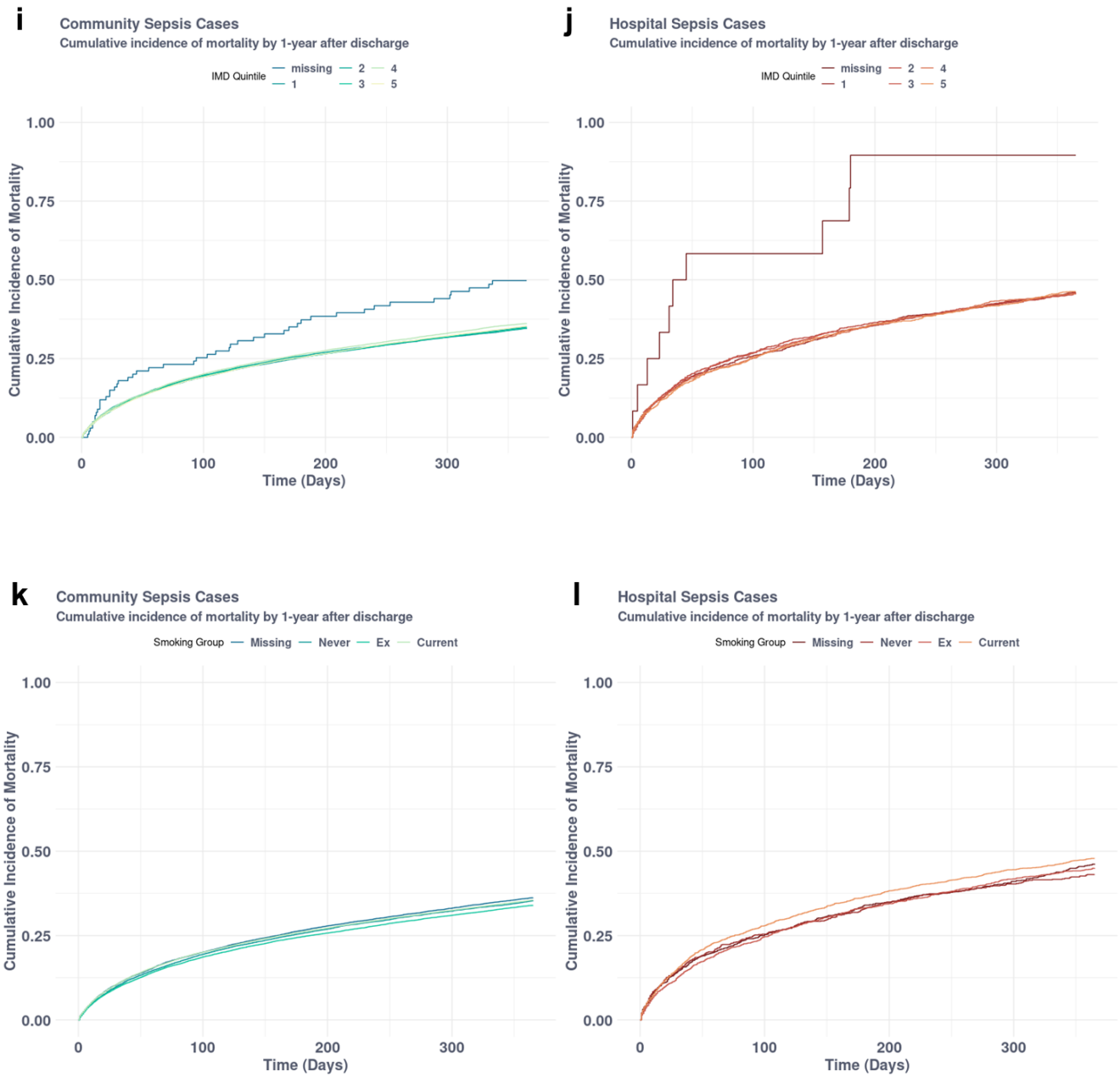


Figure S6.2 *Cumulative incidence plots for 1-year mortality after sepsis, stratified by comorbidities and prior antibiotic use*

Adjusted for antibiotic prescribing group (2a & 2b), age group (2c & 2d), BMI group (2e & 2f), Charlson comorbidity score group (2g & 2h), IMD quintile (2i & 2j) & smoking group (2k & 2l),

		Cumulative Incidence of Hospital Readmission - 1 year			
		Community Sepsis		Hospital Sepsis	
Covariate		**Cases (n = 71,330)**	**Controls (n = 417,010)**	**Cases (n = 6,064)**	**Controls (n = 32,539)**
Antibiotic Prescriptions Group	0	66.4% (65.8%, 66.9%)	31.4% (31.2%, 31.6%)	68.2% (66.4%, 70.0%)	77.1% (76.4%, 77.8%)
	1	69.2% (68.5%, 70.0%)	41.2% (40.8%, 41.6%)	67.3% (64.6%, 69.9%)	80.2% (79.2%, 81.1%)
	2	69.9% (68.9%, 70.9%)	45.7% (45.2%, 46.3%)	70.8% (67.3%, 74.0%)	81.7% (80.5%, 83.0%)
	3-4	70.8% (69.8%, 71.7%)	49.4% (48.8%, 50.0%)	70.8% (67.3%, 74.0%)	83.4% (82.2%, 84.6%)
	5-6	73.8% (72.5%, 75.1%)	52.2% (51.3%, 53.2%)	69.7% (64.1%, 74.6%)	86.7% (84.9%, 88.3%)
	7+	74.4% (73.2%, 75.5%)	55.0% (54.1%, 55.9%)	68.3% (63.5%, 72.6%)	86.8% (85.3%, 88.2%)
Age Group	60-74	71.9% (71.3%, 72.5%)	27.1% (26.8%, 27.3%)	74.6% (72.5%, 76.6%)	82.8% (82.0%, 83.5%)
	75-84	70.1% (69.6%, 0.7%)	38.0% (37.8%, 38.3%)	70.1% (68.3%,71.9%)	81.1% (80.4%, 81.8%)
	85-94	65.9% (65.2%, 66.5%)	45.1% (44.8%, 45.3%)	62.6% (60.1%, 64.9%)	77.5% (76.6%, 78.4%)
	>95	58.2% (56.2%, 60.2%)	43.0% (42.1%, 43.9%)	49.9% (42.4%, 57.0%)	67.3% (64.4%, 70.0%)
BMI (kg/m^2)	missing	67.7% (67.2%, 68.2%)	36.4% (36.2%, 36.7%)	68.0% (66.2%, 69.6%)	78.9% (78.3%, 79.6%)
	<18.5	64.8% (62.1%, 67.3%)	45.3% (44.0%, 46.7%)	59.9% (50.0%, 68.4%)	77.2% (73.5%, 80.4%)
	18.5-24	69.7% (68.8%, 70.5%)	38.2% (37.8%, 38.5%)	66.7% (63.5%, 69.7%)	80.6% (79.4%, 81.6%)
	25-30	70.7% (70.0%, 71.5%)	36.4% (36.1%, 36.7%)	70.5% (67.7%, 73.0%)	81.4% (80.4%, 82.3%)
	>30	71.2% (70.4%, 72.1%)	36.6% (36.2%, 37.0%)	72.8% (69.5%, 75.9%)	82.7% (81.4%, 83.8%)
Smoking	missing	66.6% (66.1%, 67.2%)	34.4% (34.2%, 34.7%)	67.2% (65.2%, 69.1%)	77.9% (77.1%, 78.6%)
	0 (never)	68.7% (67.9%, 69.5%)	37.3% (37.0%, 37.7%)	67.3% (64.3%, 70.1%)	80.1% (79.0%, 81.1%)
	1(ex)	71.9% (71.0%, 72.8%)	40.2% (39.8%, 40.7%)	69.6% (66.3%, 72.7%)	82.4% (81.3%, 83.5%)
	2 (current)	71.0% (70.4%, 71.6%)	38.6% (38.3%, 38.9%)	71.0% (68.8%, 73.0%)	81.7% (81.0%, 82.5%)
of Multiple Deprivation	missing	69.3% (58.8%, 77.6%)	47.5% (46.2%, 48.9%)	-	86.3% (72.4%, 93.5%)
	1	68.5% (67.8%, 69.2%)	35.2% (34.9%, 35.5%)	67.6% (64.8%, 70.1%)	78.4% (77.4%, 79.3%)
	2	68.4% (67.7%, 69.2%)	36.1% (35.8%, 36.4%)	66.6% (63.8%, 69.1%)	79.5% (78.5%, 80.5%)
	3	69.5% (68.7%, 70.2%)	36.6% (36.3%, 37.0%)	70.8% (68.0%, 73.3%)	80.3% (79.3%, 81.2%)
	4	69.7% (68.9%, 70.5%)	37.7% (37.4%, 38.1%)	69.2% (66.4%, 71.8%)	81.0% (79.9%, 81.9%)
	5 (most deprived)	69.5% (68.7%, 70.4%)	38.9% (38.5%, 39.3%)	69.8% (67.0%, 72.3%)	82.1% (81.0%, 83.1%)
Charlson comorbidity score	0	63.6% (62.7%, 64.5%)	25.3% (25.1%, 25.5%)	64.7% (61.5%, 67.8%)	72.3% (71.0%, 73.6%)
	1-2	67.4% (66.8%, 68.0%)	37.2% (37.0%, 37.5%)	67.5% (65.3%, 69.5%)	78.3% (77.6%, 79.1%)
	3-4	70.6% (69.9%, 71.2%)	45.5% (45.2%, 45.8%)	69.6% (67.4%, 71.8%)	82.5% (81.7%, 83.3%)
	5-6	73.7% (72.8%, 74.6%)	51.9% (51.3%, 52.4%)	72.7% (69.6%, 75.6%)	84.7% (83.6%, 85.7%)
	7+	74.3% (73.2%, 75.4%)	60.8% (60.0%, 61.7%)	71.2% (66.9%, 75.0%)	86.2% (84.8%, 87.4%)

Table S6.2 *Cumulative incidence of hospital readmission at 1-year, by comorbidities, demographics & prior antibiotic use.* Mortality has been accounted for as a competing risk.

BOTH		Kaplan-Meier Adjusted Antibiotic Probability - 1 year			
		Community Sepsis		Hospital Sepsis	
Covariate		Cases (n = 71,330)	Controls (n = 417,010)	Cases (n = 6,064)	Controls (n = 32,539)
Antibiotic Prescriptions Group	0	47.8%	72.9%	45.6%	56.4%
	1	32.9%	50.8%	36.6%	39.4%
	2	25.0%	37.7%	29.5%	29.8%
	3-4	16.8%	25.0%	18.2%	19.8%
	5-6	10.5%	13.1%	10.9%	11.3%
	7+	5.6%	5.2%	7.8%	6.0%
Age Group	60-74	34.8%	67.7%	35.6%	42.5%
	75-84	32.5%	59.4%	33.7%	40.3%
	85-94	30.0%	51.9%	34.8%	38.5%
	>95	27.5%	42.8%	40.1%	35.2%
BMI (kg/m^2)	<18.5	28.4%	47.2%	36.6%	34.1%
	18.5-24	33.8%	59.0%	37.7%	41.3%
	25-30	32.3%	60.1%	32.8%	39.3%
	>30	29.2%	57.1%	26.4%	39.1%
Smoking	0 (never)	31.8%	58.1%	30.7%	40.3%
	1(ex)	29.6%	55.2%	32.3%	37.3%
	2 (current)	31.9%	57.4%	33.9%	38.3%
Index of Multiple Deprivation	1	33.1%	61.0%	35.5%	42.0%
	2	32.6%	60.1%	33.3%	41.5%
	3	32.9%	59.5%	33.2%	40.7%
	4	31.8%	59.0%	35.6%	39.1%
	5 (most deprived)	32.0%	57.4%	35.4%	38.0%
Charlson comorbidity score	0	43.2%	71.9%	44.4%	51.9%
	1-2	34.0%	57.3%	35.3%	42.5%
	3-4	29.4%	50.4%	31.2%	36.8%
	5-6	25.6%	45.5%	30.8%	33.2%
	7+	24.4%	39.8%	31.1%	32.0%

Table S6.3 *Kaplan-Meier adjusted probabilities of no antibiotic prescription at 1-year, stratified by comorbidities, demographics & prior antibiotic use*

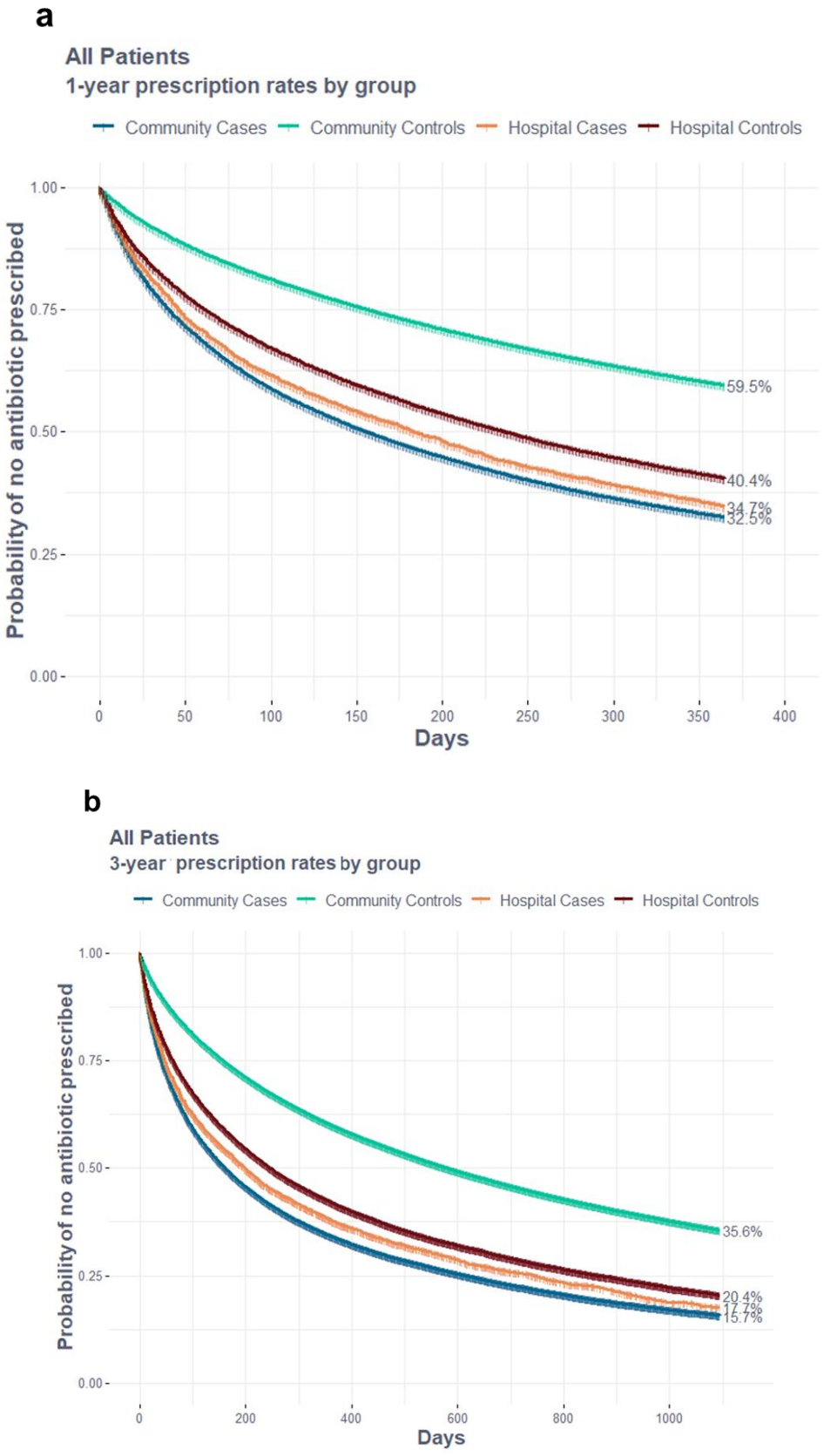


Figure S6.3 *Kaplan-Meier survival curves for 1-year (a) and 3-year (b) probabilities of not being prescribed an antibiotic, stratified by case/control group*

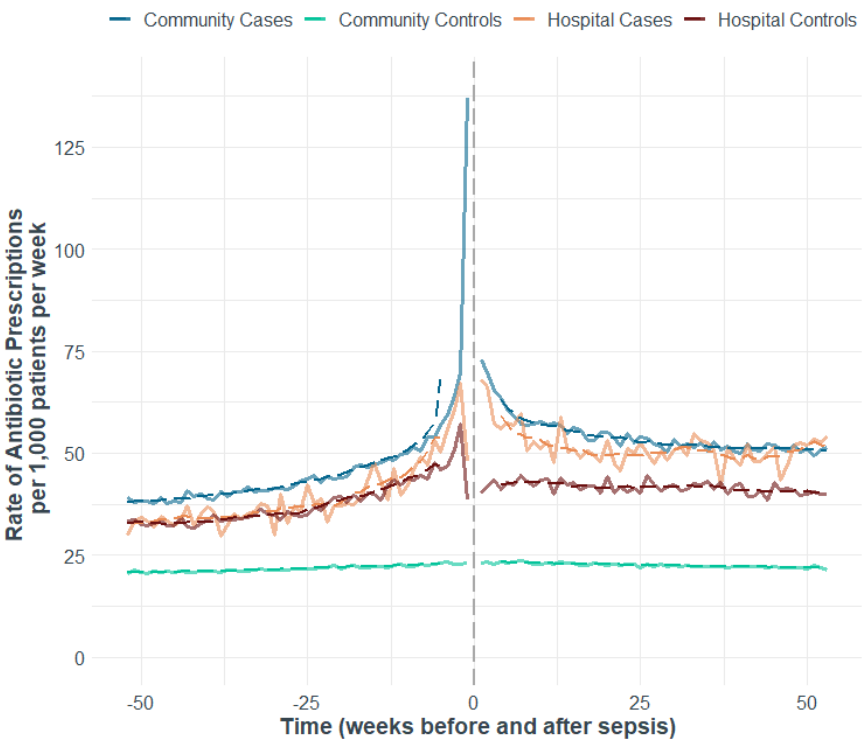


Figure S6.4 *Rate of antibiotic prescriptions (per 1,000 patients per week) in the 3-year period before and after sepsis*

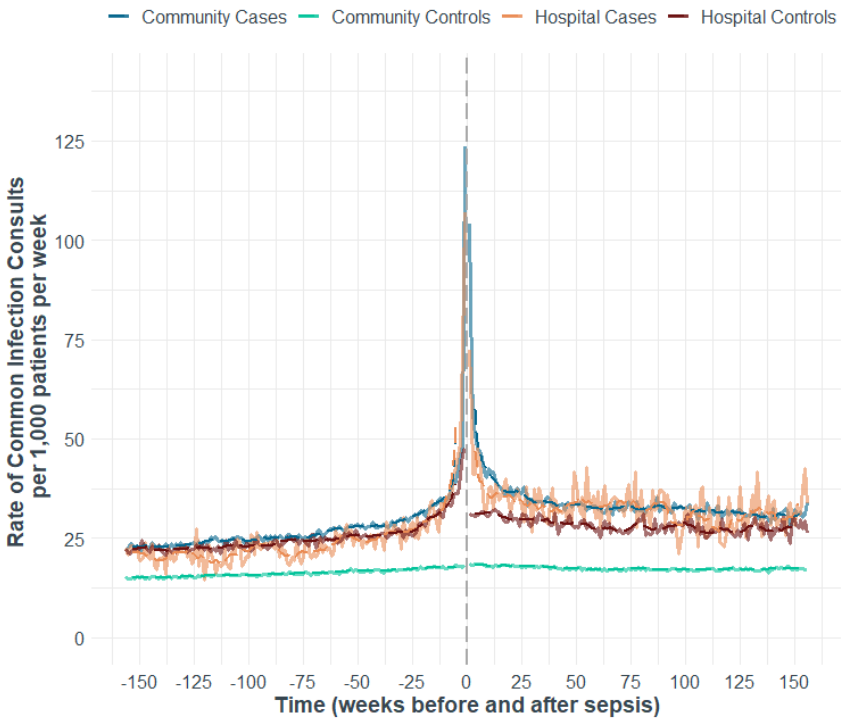


Figure S6.5 *Rate of consultations for common infections (per 1,000 patients per week) in the 3-year period before and after sepsis*

Community cohort		**1 year mortality**						**3 year mortality**					
n = 488,340		Un-adjusted			Adjusted			Un-adjusted			Adjusted		
		HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Group	ref Control	-	-	-	-	-	-	-	-	-	-	-	-
	Case	3.41	3.36, 3.47	<0.001	2.88	2.84, 2.93	<0.001	2.45	2.42, 2.48	<0.001	2.08	2.06, 2.11	<0.001
Sex	ref - Male	-	-	-	-	-	-	-	-	-	-	-	-
	Female	0.98	0.96, 0.99	<0.001	0.82	0.81, 0.83	<0.001	0.99	0.98, 1.00	0.024	0.82	0.81, 0.83	<0.001
Age at index		1.07	1.07, 1.07	<0.001	1.06	1.06, 1.06	<0.001	1.08	1.08, 1.08	<0.001	1.07	1.07, 1.07	<0.001
BMI (kg/m^2)	<18.5	2.22	2.12, 2.32	<0.001	1.86	1.78, 1.95	<0.001	2.13	2.05, 2.20	<0.001	1.79	1.73, 1.85	<0.001
	ref - 18.5-24	-	-	-	-	-	-	-	-	-	-	-	-
	25-30	0.67	0.65, 0.69	<0.001	0.73	0.71, 0.75	<0.001	0.68	0.67, 0.69	<0.001	0.74	0.73, 0.75	<0.001
	>30	0.59	0.57, 0.61	<0.001	0.64	0.62, 0.66	<0.001	0.60	0.58, 0.61	<0.001	0.66	0.65, 0.68	<0.001
	missing	1.10	1.07, 1.12	<0.001	1.32	1.30, 1.35	<0.001	1.09	1.08, 1.11	<0.001	1.31	1.30, 1.33	<0.001
Smoking status	ref - Non-smoker	-	-	-	-	-	-	-	-	-	-	-	-
	Ex-smoker (1)	1.01	0.98, 1.04	0.5	1.01	0.98, 1.04	0.50	1.01	0.99, 1.03	0.3	1.02	1.00, 1.04	0.013
	Current-smoker (2)	0.94	0.92, 0.96	<0.001	1.06	1.03, 1.08	<0.001	0.94	0.93, 0.96	<0.001	1.08	1.06, 1.10	<0.001
	Missing	0.91	0.89, 0.93	<0.001	0.96	0.94, 0.98	<0.001	0.91	0.90, 0.93	<0.001	0.95	0.94, 0.97	<0.001
IMD quintile	ref - 1 (least deprived)	-	-	-	-	-	-	-	-	-	-	-	-
	2	1.07	1.05, 1.10	<0.001	1.06	1.03, 1.08	<0.001	1.06	1.04, 1.07	<0.001	1.05	1.03, 1.06	<0.001
	3	1.08	1.06, 1.11	<0.001	1.07	1.05, 1.10	<0.001	1.09	1.08, 1.11	<0.001	1.08	1.07, 1.10	<0.001
	4	1.16	1.14, 1.19	<0.001	1.16	1.14, 1.19	<0.001	1.15	1.14, 1.17	<0.001	1.16	1.14, 1.18	<0.001
	5 (most deprived)	1.18	1.15, 1.20	<0.001	1.18	1.16, 1.21	<0.001	1.19	1.17, 1.21	<0.001	1.21	1.19, 1.23	<0.001
	Missing	2.88	2.74, 3.02	<0.001	2.19	2.08, 2.30	<0.001	2.55	2.46, 2.65	<0.001	1.77	1.70, 1.84	<0.001
Charlson comorbidity score	ref - 0	-	-	-	-	-	-	-	-	-	-	-	-
	1-2	2.12	2.07, 2.17	<0.001	1.63	1.59, 1.66	<0.001	1.98	1.95, 2.01	<0.001	1.58	1.55, 1.60	<0.001
	3-4	3.01	2.94, 3.08	<0.001	1.99	1.94, 2.04	<0.001	2.78	2.73, 2.82	<0.001	1.93	1.90, 1.96	<0.001
	5-6	3.75	3.65, 3.85	<0.001	2.32	2.26, 2.39	<0.001	3.46	3.39, 3.52	<0.001	2.28	2.24, 2.32	<0.001
	>7	5.99	5.81, 6.18	<0.001	3.60	3.49, 3.72	<0.001	5.17	5.06, 5.29	<0.001	3.39	3.31, 3.47	<0.001
Prior antibiotic prescribing group	ref - 0	-	-	-	-	-	-	-	-	-	-	-	-
	1	1.64	1.61, 1.67	<0.001	1.31	1.28, 1.33	<0.001	1.49	1.47, 1.51	<0.001	1.24	1.22, 1.26	<0.001
	2	2.05	2.00, 2.10	<0.001	1.46	1.42, 1.49	<0.001	1.84	1.81, 1.87	<0.001	1.39	1.37, 1.42	<0.001
	3-4	2.50	2.44, 2.56	<0.001	1.62	1.58, 1.66	<0.001	2.20	2.16, 2.23	<0.001	1.54	1.52, 1.57	<0.001
	5-6	2.86	2.77, 2.95	<0.001	1.73	1.68, 1.79	<0.001	2.53	2.47, 2.59	<0.001	1.67	1.64, 1.72	<0.001
	>7	3.21	3.12, 3.31	<0.001	1.92	1.87, 1.98	<0.001	2.81	2.75, 2.87	<0.001	1.85	1.81, 1.89	<0.001

Table S6.4 *Hazard ratios, confidence intervals and p-values from Cox proportional hazards model for 1-year and 3-year mortality in the community cohort*

Hospital cohort		**1 year mortality**						**3 year mortality**					
n = 38,603		Un-adjusted			Adjusted			Un-adjusted			Adjusted		
		HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Group	ref Control	-	-	-	-	-	-	-	-	-	-	-	-
	Case	1.92	1.84, 2.01	<0.001	1.91	1.83, 2.00	<0.001	1.67	1.61, 1.73	<0.001	1.67	1.61, 1.73	<0.001
Sex	ref - Male	-	-	-	-	-	-	-	-	-	-	-	-
	Female	0.82	0.79, 0.85	<0.001	0.73	0.70, 0.76	<0.001	0.76	0.73, 0.78	<0.001	0.75	0.73, 0.77	<0.001
Age at index		1.05	1.05, 1.05	<0.001	1.05	1.05, 1.05	<0.001	1.05	1.05, 1.06	<0.001	1.05	1.05, 1.06	<0.001
BMI (kg/m^2)	<18.5	1.64	1.45, 1.84	<0.001	1.68	1.49, 1.90	<0.001	1.58	1.42, 1.74	<0.001	1.59	1.43, 1.76	<0.001
	ref - 18.5-24	-	-	-	-	-	-	-	-	-	-	-	-
	25-30	0.75	0.70, 0.80	<0.001	0.78	0.73, 0.83	<0.001	0.76	0.72, 0.80	<0.001	0.79	0.75, 0.83	<0.001
	>30	0.63	0.59, 0.68	<0.001	0.71	0.66, 0.76	<0.001	0.65	0.61, 0.69	<0.001	0.73	0.69, 0.77	<0.001
	missing	1.02	0.97, 1.08	0.4	1.14	1.08, 1.20	<0.001	1.01	0.97, 1.06	0.5	1.15	1.10, 1.20	<0.001
Smoking status	ref - Non-smoker	-	-	-	-	-	-	-	-	-	-	-	-
	Ex-smoker (1)	0.97	0.90, 1.03	0.30	0.98	0.91, 1.04	0.50	0.99	0.94, 1.04	0.60	0.99	0.94, 1.04	0.60
	Current-smoker (2)	0.95	0.90, 1.01	0.09	1.02	0.96, 1.08	0.50	1.04	0.99, 1.08	0.11	1.03	0.99, 1.08	0.13
	Missing	0.94	0.89, 1.00	0.042	0.95	0.90, 1.01	0.10	0.96	0.92, 1.00	0.071	0.96	0.92, 1.00	0.064
IMD quintile	ref - 1 (least deprived)	-	-	-	-	-	-	-	-	-	-	-	-
	2	0.97	0.92, 1.03	0.30	0.97	0.92, 1.03	0.40	1.01	0.96, 1.05	0.80	1.00	0.96, 1.05	0.80
	3	1.03	0.98, 1.09	0.30	1.05	0.99, 1.11	0.12	1.04	1.00, 1.09	0.073	1.04	0.99, 1.09	0.088
	4	1.04	0.98, 1.11	0.20	1.07	1.01, 1.13	0.029	1.10	1.05, 1.15	<0.001	1.09	1.05, 1.15	<0.001
	5 (most deprived)	1.06	1.00, 1.13	0.038	1.12	1.05, 1.18	<0.001	1.16	1.11, 1.22	<0.001	1.16	1.10, 1.21	<0.001
	Missing	1.30	0.86, 1.97	0.20	1.37	0.91, 2.06	0.14	1.54	1.13, 2.11	0.006	1.56	1.14, 2.13	0.005
Charlson comorbidity score	ref - 0	-	-	-	-	-	-	-	-	-	-	-	-
	1-2	1.37	1.29, 1.47	<0.001	1.31	1.22, 1.40	<0.001	1.37	1.30, 1.44	<0.001	1.36	1.29, 1.43	<0.001
	3-4	1.63	1.52, 1.74	<0.001	1.48	1.38, 1.58	<0.001	1.54	1.46, 1.63	<0.001	1.54	1.46, 1.63	<0.001
	5-6	1.88	1.75, 2.03	<0.001	1.70	1.58, 1.83	<0.001	1.80	1.70, 1.91	<0.001	1.80	1.70, 1.91	<0.001
	>7	2.48	2.29, 2.68	<0.001	2.41	2.22, 2.61	<0.001	2.58	2.42, 2.75	<0.001	2.59	2.43, 2.76	<0.001
Prior antibiotic prescribing group	ref - 0	-	-	-	-	-	-	-	-	-	-	-	-
	1	1.14	1.08, 1.19	<0.001	1.08	1.03, 1.13	0.003	1.06	1.02, 1.10	0.006	1.05	1.01, 1.10	0.009
	2	1.33	1.26, 1.41	<0.001	1.24	1.17, 1.31	<0.001	1.19	1.14, 1.25	<0.001	1.19	1.14, 1.25	<0.001
	3-4	1.35	1.27, 1.43	<0.001	1.24	1.17, 1.32	<0.001	1.23	1.17, 1.29	<0.001	1.22	1.17, 1.28	<0.001
	5-6	1.37	1.26, 1.48	<0.001	1.26	1.16, 1.37	<0.001	1.30	1.22, 1.39	<0.001	1.29	1.21, 1.38	<0.001
	>7	1.39	1.30, 1.50	<0.001	1.35	1.26, 1.46	<0.001	1.41	1.33, 1.50	<0.001	1.41	1.33, 1.49	<0.001

Table S6.5 *Hazard ratios, confidence intervals and p-values from Cox proportional hazards model for 1-year and 3-year mortality in the hospital cohort*

Community cohort		**1 year readmission**						**3 year readmission**					
n = 488,340		Un-adjusted			Adjusted			Un-adjusted			Adjusted		
		HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Group	ref Control	-	-	-	-	-	-	-	-	-	-	-	-
	Case	3.03	3.00,3.07	<0.001	2.50	2.47,2.53	<0.001	2.29	2.27,2.32	<0.001	1.93	1.90,1.95	<0.001
Sex	ref - Male	-	-	-	-	-	-	-	-	-	-	-	-
	Female	0.92	0.91,0.93	<0.001	0.88	0.87,0.89	<0.001	0.94	0.93,0.94	<0.001	0.9	0.89,0.91	<0.001
Age at index		1.02	1.02,1.02	<0.001	1.01	1.01,1.01	<0.001	1.02	1.02,1.02	<0.001	1.01	1.01,1.01	<0.001
BMI (kg/m^2)	<18.5	1.22	1.18,1.27	<0.001	1.07	1.03,1.112	<0.001	1.1	1.07,1.14	<0.001			
	ref - 18.5-24	-	-	-	-	-	-	-	-	-	-	-	-
	25-30	0.96	0.94,0.97	<0.001	0.97	0.95,0.98	<0.001	0.98	0.96,0.99	<0.001			
	>30	1.01	1.00,1.03	0.16	0.96	0.95,0.98	<0.001	1.02	1.01,1.04	0.001			
	missing	0.95	0.94,0.96	<0.001	1.04	1.02,1.05	<0.001	0.94	0.93,0.95	<0.001			
Smoking status	ref - Non-smoker	-	-	-	-	-	-	-	-	-	-	-	-
	Ex-smoker (1)	1.12	1.10,1.14	<0.001	1.05	1.03,1.06	<0.001	1.09	1.08,1.11	<0.001	1.04	1.03,1.06	<0.001
	Current-smoker (2)	1.06	1.04,1.07	<0.001	1.02	1.00,1.03	0.012	1.01	1.00,1.03	0.007	1.01	1.00,1.02	0.24
	Missing	0.90	0.89,0.91	<0.001	0.93	0.91,0.94	<0.001	0.87	0.86,0.88	<0.001	0.91	0.90,0.92	<0.001
IMD quintile	ref - 1 (least deprived)	-	-	-	-	-	-	-	-	-	-	-	-
	2	1.04	1.02,1.05	<0.001	1.02	1.00,1.03	0.019	1.03	1.02,1.04	<0.001	1.01	1.00,1.03	0.009
	3	1.06	1.05,1.08	<0.001	1.03	1.02,1.05	<0.001	1.05	1.04,1.06	<0.001	1.03	1.01,1.04	<0.001
	4	1.10	1.09,1.12	<0.001	1.06	1.04,1.07	<0.001	1.09	1.08,1.10	<0.001	1.05	1.04,1.07	<0.001
	5 (most deprived)	1.14	1.13,1.16	<0.001	1.08	1.06,1.09	<0.001	1.12	1.11,1.14	<0.001	1.07	1.06,1.08	<0.001
	Missing	1.29	1.24,1.35	<0.001	1.21	1.16,1.26	<0.001	1.16	1.12,1.20	<0.001	1.06	1.02,1.10	0.002
Charlson comorbidity score	ref - 0	-	-	-	-	-	-	-	-	-	-	-	-
	1-2	1.63	1.61,1.65	<0.001	1.4	1.38,1.42	<0.001	1.5	1.49,1.51	<0.001	1.33	1.32,1.34	<0.001
	3-4	2.13	2.11,2.16	<0.001	1.66	1.64,1.69	<0.001	1.88	1.86,1.90	<0.001	1.55	1.53,1.56	<0.001
	5-6	2.60	2.56,2.65	<0.001	1.88	1.85,1.92	<0.001	2.23	2.20,2.26	<0.001	1.73	1.70,1.76	<0.001
	>7	3.35	3.28,3.43	<0.001	2.19	2.14,2.24	<0.001	2.65	2.60,2.70	<0.001	1.91	1.86,1.95	<0.001
Prior antibiotic prescribing group	ref - 0	-	-	-	-	-	-	-	-	-	-	-	-
	1	1.44	1.42,1.45	<0.001	1.24	1.23,1.26	<0.001	1.35	1.34,1.36	<0.001	1.21	1.20,1.22	<0.001
	2	1.67	1.65,1.70	<0.001	1.34	1.32,1.36	<0.001	1.52	1.50,1.54	<0.001	1.28	1.26,1.30	<0.001
	3-4	1.89	1.86,1.92	<0.001	1.41	1.39,1.43	<0.001	1.65	1.63,1.68	<0.001	1.31	1.29,1.33	<0.001
	5-6	2.10	2.06,2.15	<0.001	1.49	1.46,1.53	<0.001	1.81	1.78,1.85	<0.001	1.38	1.35,1.41	<0.001
	>7	2.28	2.24,2.33	<0.001	1.56	1.53,1.59	<0.001	1.92	1.89,1.96	<0.001	1.43	1.40,1.45	<0.001

Table S6.6 *Hazard ratios, confidence intervals and p-values from Fine-Grey competing risk model for 1-year and 3-year hospital readmission in the community cohort*

Hospital cohort		**1 year readmission**						**3 year readmission**					
n = 38,603		Un-adjusted			Adjusted			Un-adjusted			Adjusted		
		HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Group	ref Control	-	-	-	-	-	-	-	-	-	-	-	-
	Case	0.69	0.67, 0.71	<0.001	0.68	0.66,0.70	<0.001	0.69	0.67,0.71	<0.001	0.68	0.66,0.70	<0.001
Sex	ref - Male	-	-	-	-	-	-	-	-	-	-	-	-
	Female	0.88	0.86, 0.90	<0.001	0.92	0.90,0.94	<0.001	0.90	0.88,0.92	<0.001	0.94	0.92,0.96	<0.001
Age at index		0.99	0.98, 0.99	<0.001	0.98	0.98,0.99	<0.001	0.98	0.98,0.99	<0.001	0.98	0.98,0.98	<0.001
BMI (kg/m^2)	<18.5	0.87	0.80,0.95	0.002	0.90	0.83,0.98	0.016	0.85	0.78,0.93	<0.001			
	ref - 18.5-24	-	-	-	-	-	-	-	-	-	-	-	-
	25-30	1.04	1.00,1.08	0.043	0.98	0.95,1.02	0.39	1.05	1.02,1.09	0.003			
	>30	1.08	1.04,1.12	<0.001	0.98	0.95,1.02	0.43	1.10	1.06,1.14	<0.001			
	missing	0.94	0.91,0.97	<0.001	0.96	0.93,0.99	0.008	0.95	0.92,0.98	<0.001			
Smoking status	ref - Non-smoker	-	-	-	-	-	-	-	-	-	-	-	-
	Ex-smoker (1)	1.08	1.04, 1.12	<0.001	1.02	0.98,1.06	0.29	1.07	1.03,1.11	<0.001	1.01	0.97,1.05	0.59
	Current-smoker (2)	1.04	1.01, 1.08	0.009	1.01	0.98,1.04	0.51	1.03	1.00,1.06	0.036	1.00	0.97,1.03	0.88
	Missing	0.93	0.91, 0.96	<0.001	1.00	0.96,1.03	0.79	0.93	0.90,0.95	<0.001	0.99	0.96,1.02	0.41
IMD quintile	ref - 1 (least deprived)	-	-	-	-	-	-	-	-	-	-	-	-
	2	1.02	0.98, 1.05	0.30	1.01	0.98,1.04	0.63	1.02	0.99,1.06	0.15	1.01	0.98,1.05	0.35
	3	1.04	1.00, 1.07	0.029	1.02	0.99,1.05	0.26	1.04	1.01,1.07	0.02	1.02	0.99,1.05	0.24
	4	1.04	1.01, 1.08	0.021	1.02	0.99,1.05	0.25	1.04	1.01,1.07	0.022	1.02	0.99,1.05	0.30
	5 (most deprived)	1.04	1.01, 1.08	0.021	1.01	0.98,1.05	0.47	1.05	1.01,1.08	0.005	1.02	0.98,1.05	0.31
	Missing	1.06	0.84, 1.33	0.60	1.11	0.88,1.39	0.37	1.00	0.79,1.28	0.97	1.06	0.84,1.34	0.62
Charlson comorbidity score	ref - 0	-	-	-	-	-	-	-	-	-	-	-	-
	1-2	1.15	1.11, 1.19	<0.001	1.16	1.12,1.20	<0.001	1.13	1.10,1.17	<0.001	1.14	1.11,1.18	<0.001
	3-4	1.27	1.23, 1.32	<0.001	1.29	1.24,1.34	<0.001	1.24	1.20,1.28	<0.001	1.26	1.22,1.31	<0.001
	5-6	1.34	1.29, 1.40	<0.001	1.36	1.30,1.42	<0.001	1.29	1.24,1.34	<0.001	1.32	1.27,1.37	<0.001
	>7	1.44	1.37, 1.50	<0.001	1.42	1.35,1.49	<0.001	1.35	1.29,1.41	<0.001	1.35	1.29,1.41	<0.001
Prior antibiotic prescribing group	ref - 0	-	-	-	-	-	-	-	-	-	-	-	-
	1	1.07	1.04, 1.10	<0.001	1.06	1.03,1.09	<0.001	1.07	1.04,1.10	<0.001	1.07	1.04,1.10	<0.001
	2	1.12	1.08, 1.16	<0.001	1.10	1.06,1.14	<0.001	1.09	1.05,1.12	<0.001	1.08	1.04,1.12	<0.001
	3-4	1.14	1.11, 1.18	<0.001	1.13	1.09,1.16	<0.001	1.13	1.09,1.17	<0.001	1.12	1.08,1.16	<0.001
	5-6	1.22	1.17, 1.28	<0.001	1.20	1.14,1.25	<0.001	1.21	1.16,1.27	<0.001	1.19	1.14,1.24	<0.001
	>7	1.23	1.18, 1.28	<0.001	1.20	1.15,1.25	<0.001	1.19	1.14,1.24	<0.001	1.17	1.12,1.22	<0.001

Table S6.7 *Hazard ratios, confidence intervals and p-values from Fine-Grey competing risk model for 1-year and 3-year hospital readmission in the hospital cohort*

GOLD		Community Cohort		Hospital Cohort	
Variable		**Cases (n = 10,210)**	**Controls (n = 58,564)**	**Cases (n = 1,627)**	**Controls (n = 9,287)**
Gender, n female (%)		5,123 (50.2%)	29,468 (50.3%)	377 (47.5%)	1,983 (47.3%)
Ethnicity, n (%)	White	4,362 (94.3%)	21,470 (94.0%)	306 (95.0%)	1,357 (95.7%)
	Black	79 (1.7%)	461 (2.0%)	7 (2.2%)	18 (1.3%)
	Asian	151 (3.3%)	775 (3.4%)	9 (2.8%)	37 (2.6%)
	Other	33 (0.7%)	128 (0.6%)	0 (0.0%)	6 (0.4%)
	Missing	5,585	35,730	471	2,773
Age (years), median (IQR)		80 (73, 86)	80 (73, 86)	79 (72, 86)	79 (72, 85)
	60-74	2,999 (29.4%)	17,266 (29.5%)	267 (33.7%)	1,426 (34.0%)
	75-84	4,036 (39.5%)	23,600 (40.3%)	296 (37.3%)	1,590 (37.9%)
	85-94	2,840 (27.8%)	16,244 (27.7%)	207 (26.1%)	1,060 (25.3%)
	>95	335 (3.3%)	1,454 (2.5%)	23 (2.9%)	115 (2.7%)
BMI (kg/m^2), median (IQR)		26.6 (23.3, 30.4)	26.2 (23.4, 29.5)	26.5 (23.1, 30.1)	26.3 (23.3, 29.8)
	Low BMI (<18.5), n (%)	317 (3.8%)	1,414 (2.9%)	26 (3.9%)	121 (3.3%)
	Normal BMI (18.5-24), n (%)	2,794 (33.4%)	17,383 (35.7%)	233 (35.2%)	1,272 (35.2%)
	Overweight (25-30), n (%)	2,920 (34.9%)	19,017 (39.0%)	234 (35.3%)	1,344 (37.2%)
	Obese (>30), n (%)	2,325 (27.8%)	10,934 (22.4%)	169 (25.5%)	880 (24.3%)
	Missing, n	1,854	9,816	131	574
Smoking status, n (%)	Current	1,309 (13.5%)	6,899 (12.5%)	113 (15.2%)	596 (14.9%)
	Ex-smoker (1)	3,573 (36.9%)	18,898 (34.3%)	292 (39.4%)	1,551 (38.7%)
	Non-smoker (0)	4,800 (49.6%)	29,229 (53.1%)	337 (45.4%)	1,857 (46.4%)
	Missing	528	3,538	51	187
IMD Quintile, n (%)	1 (least deprived)	2,180 (21.4%)	14,374 (24.6%)	151 (19.1%)	996 (23.8%)
	2	2,232 (21.9%)	13,063 (22.3%)	169 (21.3%)	982 (23.4%)
	3	2,231 (21.9%)	12,388 (21.2%)	185 (23.4%)	895 (21.4%)
	4	1,943 (19.0%)	10,492 (17.9%)	158 (19.9%)	788 (18.8%)
	5 (most deprived)	1,618 (15.9%)	8,208 (14.0%)	129 (16.3%)	528 (12.6%)
	Missing	6	39	1	2
Charlson comorbidity score, median (IQR)		2.00 (1.00, 4.00)	1.00 (0.00, 3.00)	2.00 (1.00, 4.00)	2.00 (1.00, 4.00)
	0	1,764 (17.3%)	20,625 (35.2%)	142 (17.9%)	840 (20.0%)
	1-2	3,897 (38.2%)	21,790 (37.2%)	301 (38.0%)	1,616 (38.6%)
	3-4	2,745 (26.9%)	11,318 (19.3%)	220 (27.7%)	1,083 (25.8%)
	5-6	1,207 (11.8%)	3,624 (6.2%)	84 (10.6%)	424 (10.1%)
	>7	597 (5.8%)	1,207 (2.1%)	46 (5.8%)	228 (5.4%)
Comorbidity, n (%)	Cancer	2,630 (25.8%)	9,362 (16.0%)	184 (23.2%)	1,226 (29.3%)
	Cerebrovascular Disease	1,972 (19.3%)	7,196 (12.3%)	167 (21.1%)	669 (16.0%)
	COPD	1,709 (16.7%)	7,865 (13.4%)	118 (14.9%)	710 (16.9%)
	Heart Failure	1,179 (11.5%)	3,687 (6.3%)	101 (12.7%)	410 (9.8%)
	Dementia	1,207 (11.8%)	3,650 (6.2%)	83 (10.5%)	266 (6.3%)
	Diabetes	2,539 (24.9%)	8,865 (15.1%)	199 (25.1%)	817 (19.5%)
	HIV	1 (0.0%)	5 (0.0%)	0 (0.0%)	0 (0.0%)
	Liver Disease	101 (1.0%)	181 (0.3%)	8 (1.0%)	31 (0.7%)
	Renal Disease	2,955 (28.9%)	13,234 (22.6%)	228 (28.8%)	1,096 (26.2%)
	Peripheral Vascular Disease	877 (8.6%)	3,253 (5.6%)	79 (10.0%)	426 (10.2%)
	Autoimmnune Disease	1,077 (10.5%)	4,146 (7.1%)	106 (13.4%)	413 (9.9%)
	Deep Vein Thrombosis	683 (6.7%)	2,801 (4.8%)	55 (6.9%)	281 (6.7%)
	Skin Ulcer	1,211 (11.9%)	3,092 (5.3%)	85 (10.7%)	349 (8.3%)
	Coronary Heart Disease	2,400 (23.5%)	11,069 (18.9%)	189 (23.8%)	1,089 (26.0%)
	Hypertension	5,783 (56.6%)	30,668 (52.4%)	453 (57.1%)	2,288 (54.6%)

Table S6.8 *Baseline demographics and comorbidities for Gold cohort patients*

AURUM		Community Cohort		Hospital Cohort	
Variable		**Cases (n = 61,120)**	**Controls (n = 358,446)**	**Cases (n = 5,271)**	**Controls (n = 28,348)**
Gender, n female (%)		30,115 (49.3%)	176,673 (49.3%)	2,552 (48.4%)	13,880 (49.0%)
Ethnicity, n (%)	White	57,131 (95.1%)	309,761 (94.8%)	4,894 (94.6%)	26,729 (95.4%)
	Black	938 (1.6%)	5,528 (1.7%)	110 (2.1%)	442 (1.6%)
	Asian	1,509 (2.5%)	8,019 (2.5%)	130 (2.5%)	620 (2.2%)
	Other	513 (0.9%)	3,395 (1.0%)	42 (0.8%)	216 (0.8%)
	Missing	1,029	31,743	95	341
Age (years), median (IQR)		80 (73, 86)	80 (73, 86)	80 (74, 86)	80 (74, 86)
	60-74	18,286 (29.9%)	106,948 (29.8%)	1,454 (27.6%)	7,791 (27.5%)
	75-84	23,914 (39.1%)	140,995 (39.3%)	2,192 (41.6%)	11,732 (41.4%)
	85-94	16,793 (27.5%)	98,579 (27.5%)	1,451 (27.5%)	7,847 (27.7%)
	>95	2,127 (3.5%)	11,924 (3.3%)	174 (3.3%)	978 (3.4%)
BMI (kg/m^2), median (IQR)		27.0 (23.7, 30.7)	26.8 (23.7, 29.6)	27.0 (23.4, 30.1)	27.0 (23.4, 29.9)
	Low BMI (<18.5), n (%)	1,034 (3.5%)	4,114 (2.5%)	88 (3.8%)	470 (3.7%)
	Normal BMI (18.5-24), n (%)	8,647 (29.5%)	52,804 (32.3%)	706 (30.2%)	4,015 (31.2%)
	Overweight (25-30), n (%)	11,290 (38.5%)	68,606 (42.0%)	949 (40.5%)	5,225 (40.6%)
	Obese (>30), n (%)	8,371 (28.5%)	37,916 (23.2%)	598 (25.5%)	3,163 (24.6%)
	Missing, n	31,778	195,006	2,930	15,475
Smoking status, n (%)	Current	20,123 (57.1%)	110,178 (57.5%)	1,792 (58.8%)	9,392 (56.6%)
	Ex-smoker (1)	6,610 (18.8%)	33,709 (17.6%)	535 (17.6%)	3,070 (18.5%)
	Non-smoker (0)	8,484 (24.1%)	47,782 (24.9%)	721 (23.7%)	4,118 (24.8%)
	Missing	25,903	166,777	2,223	11,768
IMD Quintile, n (%)	1 (least deprived)	13,566 (22.2%)	85,944 (24.3%)	1,102 (21.0%)	6,368 (22.5%)
	2	13,070 (21.4%)	78,346 (22.2%)	1,102 (21.0%)	6,035 (21.3%)
	3	12,005 (19.7%)	69,259 (19.6%)	1,006 (19.1%)	5,933 (21.0%)
	4	11,458 (18.8%)	62,987 (17.8%)	1,000 (19.0%)	5,203 (18.4%)
	5 (most deprived)	10,925 (17.9%)	56,444 (16.0%)	1,050 (20.0%)	4,760 (16.8%)
	Missing	96	5,466	11	49
Charlson comorbidity score, median (IQR)		2.00 (1.00, 4.00)	1.00 (0.00, 3.00)	3.00 (1.00, 4.00)	3.00 (1.00, 4.00)
	0	9,555 (15.6%)	116,621 (32.5%)	777 (14.7%)	4,039 (14.2%)
	1-2	21,214 (34.7%)	128,510 (35.9%)	1,773 (33.6%)	10,048 (35.4%)
	3-4	16,882 (27.6%)	74,176 (20.7%)	1,507 (28.6%)	7,925 (28.0%)
	5-6	8,457 (13.8%)	28,089 (7.8%)	778 (14.8%)	3,890 (13.7%)
	>7	5,012 (8.2%)	11,050 (3.1%)	436 (8.3%)	2,446 (8.6%)
Comorbidity, n (%)	Cancer	17,072 (27.9%)	64,094 (17.9%)	1,398 (26.5%)	8,528 (30.1%)
	Cerebrovascular Disease	11,893 (19.5%)	47,609 (13.3%)	1,188 (22.5%)	6,024 (21.3%)
	COPD	10,606 (17.4%)	50,089 (14.0%)	914 (17.3%)	5,327 (18.8%)
	Heart Failure	8,236 (13.5%)	28,311 (7.9%)	840 (15.9%)	4,426 (15.6%)
	Dementia	7,600 (12.4%)	27,409 (7.6%)	551 (10.5%)	2,364 (8.3%)
	Diabetes	16,085 (26.3%)	60,667 (16.9%)	1,470 (27.9%)	6,573 (23.2%)
	HIV	3 (0.0%)	77 (0.0%)	1 (0.0%)	2 (0.0%)
	Liver Disease	677 (1.1%)	1,515 (0.4%)	77 (1.5%)	318 (1.1%)
	Renal Disease	18,921 (31.0%)	83,808 (23.4%)	1,720 (32.6%)	8,825 (31.1%)
	Peripheral Vascular Disease	5,732 (9.4%)	21,722 (6.1%)	524 (9.9%)	2,879 (10.2%)
	Autoimmnune Disease	6,806 (11.1%)	26,096 (7.3%)	584 (11.1%)	2,931 (10.3%)
	Deep Vein Thrombosis	138 (0.2%)	455 (0.1%)	12 (0.2%)	55 (0.2%)
	Skin Ulcer	7,417 (12.1%)	20,619 (5.8%)	668 (12.7%)	2,706 (9.5%)
	Coronary Heart Disease	14,989 (24.5%)	69,559 (19.4%)	1,419 (26.9%)	8,844 (31.2%)
	Hypertension	36,212 (59.2%)	195,218 (54.5%)	3,223 (61.1%)	17,065 (60.2%)

Table S6.9 *Baseline demographics and comorbidities for Aurum cohort patients*

	Community Sepsis		Hospital Sepsis	
	Cases (n = 10,210)	Controls (n = 58,564)	Cases (n = 793)	Controls (n = 4,191)
Cumulative incidence - mortality				
All cause 1-year	37.7% (36.8%, 38.7%)	10.0% (9.77%, 10.3%)	46.6% (42.8%, 50.2%)	24.4% (23.1%, 25.8%)
All cause 3-year	63.2% (62.1%, 64.2%)	32.3% (31.8%, 32.7%)	69.7% (66.0%, 73.2%)	48.5% (46.8%, 50.2%)
Cumulative incidence - hospital readmission				
All cause 1-year	69.2% (68.2%, 70.1%)	35.2% (34.8%, 35.6%)	69.6% (66.2%, 72.8%)	80.9% (79.6%, 82.1%)
All cause 3-year	81.0% (80.2%, 81.8%)	66.5% (66.1%, 66.9%)	78.0% (74.9%, 80.8%)	89.7% (88.7%, 90.6%)

Table S6.10 *Cumulative incidence for all-cause mortality and hospital readmission for Gold cohort patients*

	Community Sepsis		Hospital Sepsis	
	Cases (n = 61,120)	Controls (n = 358,446)	Cases (n = 5,271)	Controls (n = 28,348)
Cumulative incidence - mortality				
All cause 1-year	34.8% (34.4%, 35.2%)	13.0% (12.9%, 13.2%)	46.0% (44.5%, 47.4%)	29.2% (28.6%, 29.7%)
All cause 3-year	57.1% (56.6%, 57.5%)	33.3% (33.1%, 33.5%)	66.8% (65.4%, 68.2%)	51.1% (50.5%, 51.7%)
Cumulative incidence - hospital readmission				
All cause 1-year	69.1% (68.7%, 69.4%)	37.1% (37.0%, 37.3%)	68.6% (67.3%, 69.9%)	80.0% (79.5%, 80.5%)
All cause 3-year	81.2% (80.9%, 81.5%)	63.8% (63.6%, 64.0%)	77.9% (76.7%, 79.0%)	88.2% (87.8%, 88.6%)

Table S6.11 *Cumulative incidence for all-cause mortality and hospital readmission for Aurum cohort patients*

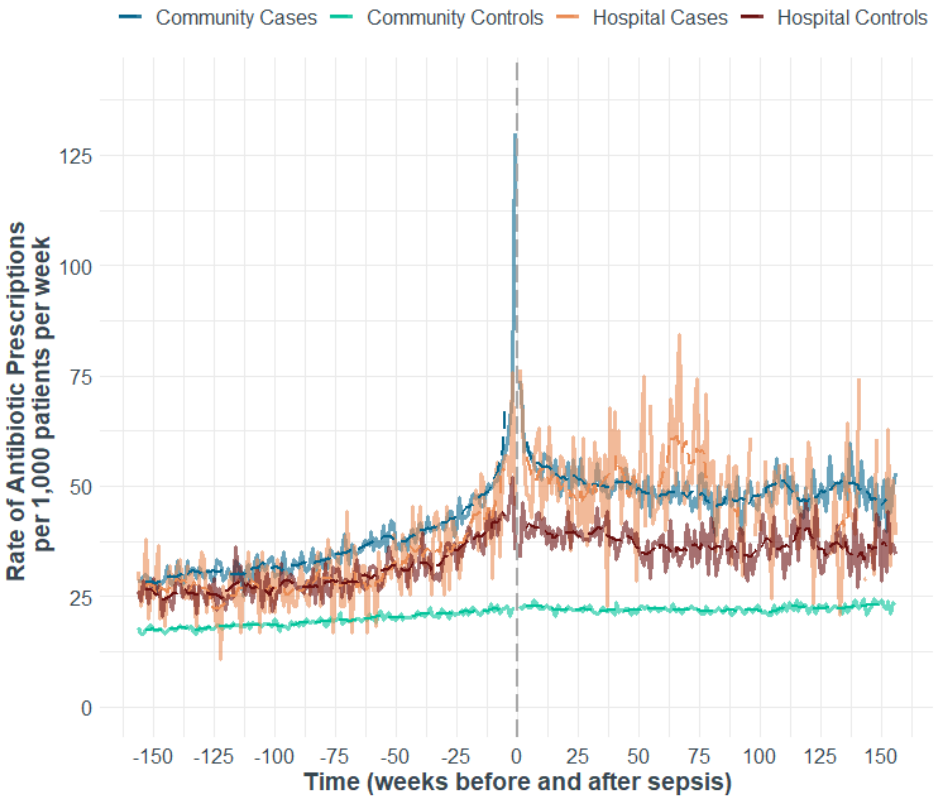


Figure S6.6 *Rates of antibiotic prescriptions per 1,000 Gold patients per week in the 3 years either side of a sepsis admission*

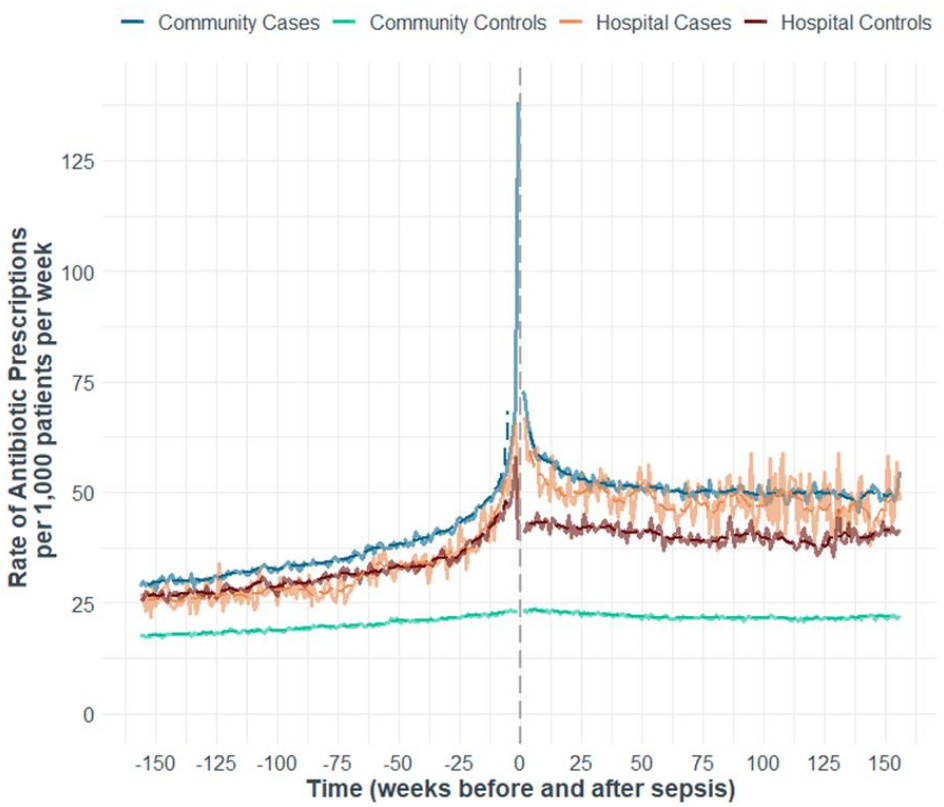


Figure S6.7 *Rates of antibiotic prescriptions per 1,000 Aurum patients per week in the 3 years either side of a sepsis admission*

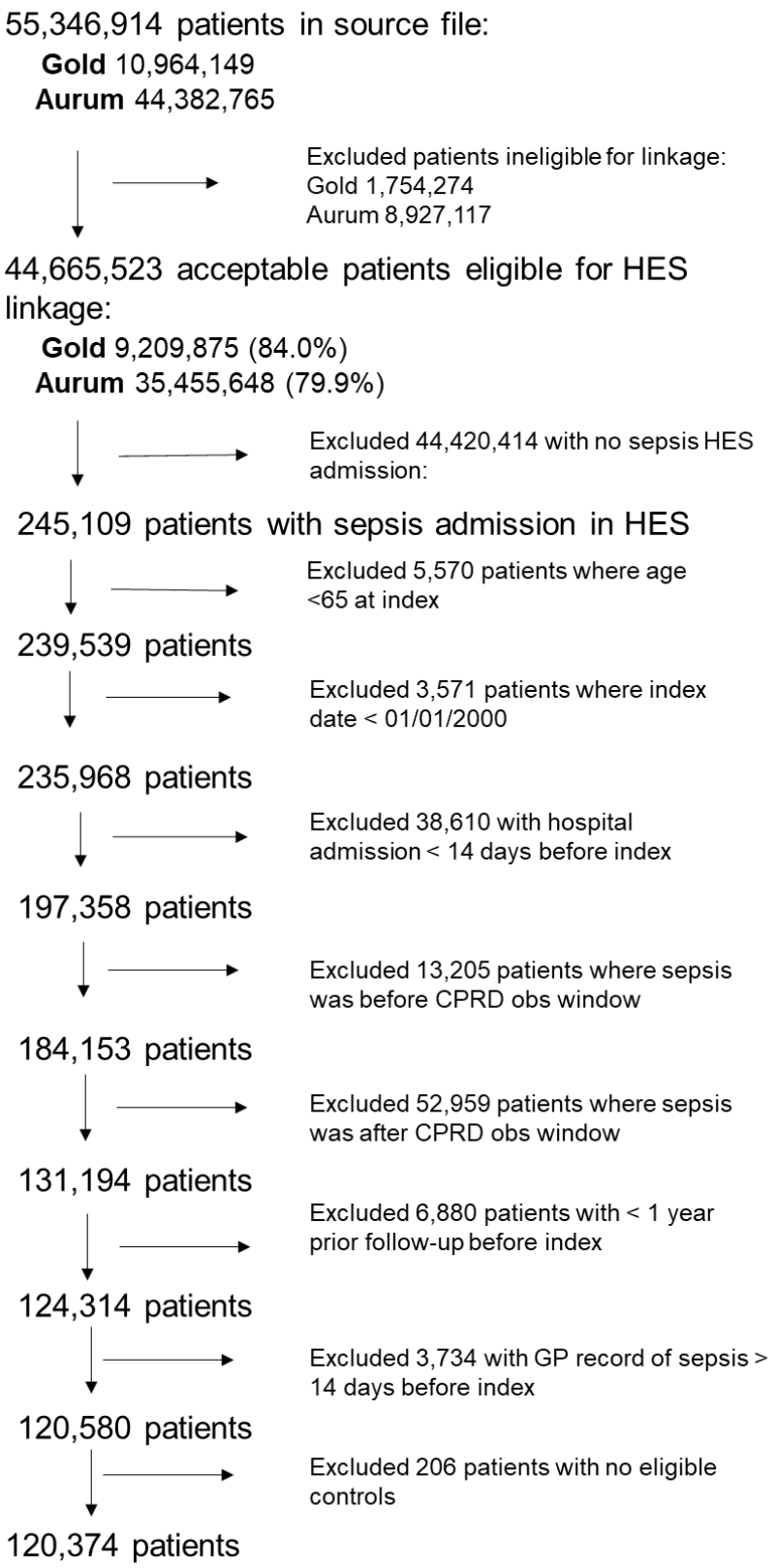


Figure S6.8 *Inclusion/exclusion flow chart for patient selection*

Chapter 7 – Discussion

7.1 Key findings

The aims of this thesis were to use sources of primary and secondary care data to explore the role of antibiotics in the sepsis pathway, including before a patient develops sepsis, during their treatment and the post-sepsis period. The specific aims for the three chapters were:

1. To evaluate the risk factors for developing sepsis, including demographics, comorbidities and antibiotic use, and to determine whether these risk factors differ between patients with community- or hospital-acquired sepsis
2. To evaluate the types and quantities of antimicrobials sepsis patients receive and to investigate the association between this and short-term mortality
3. To determine the long-term outcomes following a sepsis episode, in terms of mortality, readmission to hospital and primary care use, and to evaluate differences between community- and hospital-acquired sepsis

The key findings from the first study were that there are differences between patients who develop sepsis in the community and hospital, in terms of risk factors for development of sepsis. Comorbidity levels and prior antibiotic use increased the risk of community-acquired sepsis but with a much smaller effect on hospital-acquired sepsis.

The second study found that patients treated for sepsis are exposed to high levels of antimicrobials, both in terms of the number of courses prescribed and the number of exposure days. Patients who receive a lower number of antimicrobials but have a higher number of exposure days were at decreased risk of 30-day mortality.

In the final study, again we demonstrated differences in outcomes after surviving an episode of community- or hospital- acquired sepsis. Prior antibiotic use and comorbidity levels affect the risk of long term mortality in community-sepsis, but less so in hospital sepsis. In the period prior to sepsis the rate of antibiotic prescribing was higher in community-acquired cases than hospital-acquired cases. Following sepsis both groups saw an increase in antibiotic prescriptions, and the difference between the groups was smaller.

7.2 How my studies add knowledge

The first study using CPRD and HES data was the first to use a combination of primary and secondary care data to look at the pre-sepsis pathway. Previous studies have mostly used secondary care data only with a few using primary care data. With this combination of data

sources it means this is one of few studies that looks at how antibiotics in primary care affects risk of developing sepsis.

By distinguishing between community- and hospital- acquired sepsis patients and the use of separate control groups for the subgroups is another unique feature of this study. What has not previously been studied much is whether there are differences in risk factors between the two groups. We have shown that levels of comorbidity and antibiotic use are associated with increased risk of sepsis in patients who develop it in the community, but not in patients who develop it in the hospital.

Whilst the timing of antibiotics has been widely studied in relation to outcomes there are few studies looking at overall exposure and how that affects mortality, which is what the MIMIC-III study focused on. The use of two different antimicrobial exposure measures showed that patients who receive more courses, but are exposed on a fewer number of days have a higher risk of in-hospital mortality. Whilst they may contradict each other it could be to do with the type of infection the patient had or whether they were treated with an empirical antimicrobial or one specifically targeting the infecting organism. The study highlighted the complexities of using sources of data around prescribing in secondary care.

For the third paper, also using CPRD and HES data, this again was one of the first studies linking primary and secondary care data to assess longer-term outcomes. Most of the existing literature focus on mortality and use of secondary care or residential care facilities. This is the first study to look at primary care use following a sepsis episode. The differences in short-term outcomes between community- and hospital-acquired sepsis in terms of illness severity and mortality have been previously reported, patients who acquire sepsis in hospital consistently are more severely ill and at higher risk of in-hospital mortality. However, there were no studies looking at differences in longer-term outcomes. By including control patients and comparing the two sepsis groups we have added further to the strength of the evidence of differences in community- and hospital-acquired sepsis.

7.3 Strengths and limitations

The main strengths and limitations of these studies lie around the data sources used. Whilst we were able to access data from large cohorts each data source was limited to a specific area, for example MIMIC-III is majority ICU data.

7.3.1 Strengths

A major strength of the MIMIC-III database is the fact that is an extremely comprehensive dataset, with all aspects of a patients ICU care recorded and time-stamped. All of the variables were clearly explained in the accompanying data dictionaries, and compared to the CPRD & HES data the process of gaining access to the data was much quicker and had no cost associated with it. Additionally, the database contains a large number of patients and although I could only use one of the two databases and it was restricted to a single centre, in the study we had a cohort of over 8,600 patients.

With the availability of observations and measurements data as well as the coded diagnostic information this meant I was able to identify patients using the Sepsis-3 criteria as well as through ICD-10 codes. As discussed in the background of this thesis previous studies have assessed how the method of identifying sepsis in electronic health records can influence the cohort size and severity of disease. Definitions and criteria of sepsis have changed over the years and so have the relevant ICD codes. Whether or not a patient has a code in their record for sepsis heavily depends on the definition at the time and opinion of the clinician/s treating them, whereas retrospectively applying criteria uniformly across the cohort reduces that potential bias.

The comprehensive data in MIMIC-III around drug prescriptions and IV administrations of drugs was a significant advantage. One of the limitations with using prescriptions data in retrospective studies is that whilst you may have the time period for which the prescription is valid you do not normally know how frequently or for how long the patient actually received the drug for. An advantage of the MIMIC-III data, therefore, is that for the drugs given to patients via an IV whilst they were in the ICU (which accounted for the majority of all drugs prescribed in ICU) it was possible to see how many doses and how frequently they were administered. As EHR systems become more widely used in secondary care in the UK this opens up more opportunities with granular data around antibiotic exposure.

Another advantage of the MIMIC-III database is that the researchers who have developed it place a strong emphasis on open-source code and provide a wealth of code and data tables for other researchers to use[1]. For example, one of the first pieces of research done using the data and by researchers with MIMIC-III they were looking specifically at sepsis patients and how to identify them using the different criteria mentioned below[2]. The code they used as well as a dataset detailing the patients that make up the different cohorts were available and researchers encouraged to make use of them. Algorithms for calculating measures such as the Elixhauser comorbidity index and SOFA score were also provided.

The major strength of using CPRD data is that it was possible to link primary care data with secondary care HES records, which was a unique aspect of the two studies. This was advantageous in terms of identifying sepsis patients in hospital admissions and not relying on primary care record of sepsis events, which has been shown to produce quite different cohorts[3]. The majority of people who develop sepsis will be treated in secondary care which may not be recorded in primary care records. It also meant we were able to use primary care records for the prior- and post- sepsis follow-up periods. As the majority of patients will develop sepsis in the community the interactions with primary care clinicians in the preceding weeks or months may be an important part of the pathway into sepsis. By only using HES records it would not have been possible to look at how prior antibiotic use affects the risk and outcomes of sepsis. Whilst there have been studies assessing the long-term effects of sepsis these have mainly focussed on readmission to secondary care or the need for additional care in a residential or nursing facility. Without the linkage between primary and secondary care and ONS mortality data it would not have been possible to address the gap in the literature for the impact of sepsis on primary care.

Another advantage of using CPRD/HES records is the availability of two different datasets within CPRD, Aurum and Gold, which meant I could validate any findings from one cohort in the other. Both of the datasets within CPRD have been shown to be broadly representative of the UK population[4,5]. We found very similar results in the two cohorts and for the manuscripts have amalgamated the two together. The results for the separate datasets can be found in the supplementary materials for the relevant papers.

As well as those strengths of the specific data sources there are additional advantages to retrospective observational studies using electronic health record data. One such advantage is the large patient cohorts I was able to include in all three studies. Using these databases gives researchers access to much larger cohorts than prospective cohort studies or RCTs would. It also means there is a broader range of variables available. Data collected for RCTs will be limited to variables of interest to the trial outcomes, whereas accessing EHR data retrospectively usually means there is more information available and the possibility to define multiple outcomes of interest.

7.3.2 Limitations

One of the limitations of the MIMIC-III dataset was that as the dataset only contains data from ICU patients, there was no opportunity within the MIMIC-III data to differentiate between community- and hospital-acquired patients. The information available for the patients either side of their ICU stay in the wider hospital was limited, which made estimating the total

antimicrobial burden impossible. Additionally, as the data is collected from a single US hospital it is perhaps not generalizable to other areas. Ideally, it would have been possible to access a UK source of secondary care data with a similar level of granularity to MIMIC-III and a similar national coverage like the CPRD and HES data.

MIMIC-III only contained data from patients who have been admitted to an ICU, so only captured a subset of patients in hospital with sepsis, and potentially those with more severe disease. Another drawback of MIMIC-III is the way in which they have anonymised the data, to protect patient's identities they have shifted the dates into the future, between 2100 and 2200. Whilst timelines for each patient has been preserved, i.e. if a patient has been admitted multiple times then the time difference between these admissions is accurate, it does mean that it is not possible to use MIMIC-III for certain research questions, for example investigating whether the incidence or mortality of sepsis has changed over time.

There are disadvantages to the use of CPRD in my studies. Firstly, by linking the GP data to the HES admissions data this did reduce my sample size. CPRD collects data from GP practices from across the UK, however, only a proportion of those in England are eligible for linkage to HES. Despite this I still had a relatively large sample size and is outweighed by the advantage gained from being able to link the data.

Secondly, as CPRD is mainly GP data, the data available in HES was fairly limited. There was no prescriptions, microbiological testing or clinical measurements data available. There were diagnostic codes and procedural codes but it was difficult to group these in a meaningful way. This was particularly important for the patients who acquired sepsis in hospital, as it is likely that there are additional risk factors such as the site and type of initial infection, whether they had undergone an invasive surgical procedure or if they had a catheter or in-dwelling device fitter. Whether or not the patient had received any antibiotics and what type in the initial period of their hospital stay could also have an impact of their risk of sepsis.

Additionally, as not all UK GP's contribute to CPRD and not all patients registered with GP's agree to share their data there were patients who were lost to follow-up. Individual patients may leave a GP or remove their consent for their data to be shared, and whole practices may unregister from CPRD. It is important to take into account this loss-to-follow-up in any analysis using the data.

Another major limitation of the studies using CPRD and HES was the issue around limiting the age of the cohort to patients over the age of 65 only. This introduced bias in the studies as age is a known risk factor for developing sepsis, the results may not be generalizable to all age groups. This decision was largely made to ensure that the analyses for the two studies

could be completed within my PhD programme, as there had already been significant delays caused by the COVID-19 pandemic and accessing the data from CPRD.

The definitions of community- and hospital- acquired sepsis and their respective control groups are another limitation with those studies and a potential form of selection bias. To strengthen the findings from these studies multiple control groups should have been used for both community-acquired and hospital-acquired sepsis patients, including non-hospitalised and hospitalised controls. This would help determine if the findings in our studies are as a result of sepsis or hospitalisation in general. Additionally, conducting sensitivity analyses varying the time cut-off for community- and hospital-acquired sepsis would have been useful to see if that had any effect on findings, given that the proportion of community- acquired sepsis patients was higher than in most other studies.

There are limitations to observational research using EHR data, mainly due to missing data and bias. Unlike in prospective studies or RCTs where specific information is collected at defined time points the information contained in EHR data is dependent on what information was seen to be relevant to the clinician at the time. There is an inherent bias in EHR data towards sicker patients, who have more frequent interactions with the healthcare system. As discussed in the methods chapter there are different types of missing data and different approaches to dealing with them. Complete case analysis would reduce the sample size and increase the bias towards sicker patients. Multiple imputation can be computationally intensive and is not appropriate when data is missing not at random. The two CPRD/HES studies used a missing indicator approach, which is simpler than multiple imputation but has been shown to result in biased estimates and is therefore a limitation of these studies. In future it would be interesting to repeat the analysis using a multiple imputation approach and see how those results compare to those from the missing indicator approach.

Another issue with this type of research is the problem of unmeasured or residual confounding. Whilst I was able to access large datasets with a comprehensive set of variables there were certain covariates that I did not include in the analyses. The MIMIC-III dataset only contained data from within a hospital admission, so I was not able to assess the levels of primary care antibiotic use prior to their sepsis admission. For the CPRD/HES studies there was limited data in the HES records, with no secondary care antibiotic use data available for these patients. Additionally, whilst the procedures codes were provided in the HES records given the time constraints for the project I did not assess which procedures patients had undertaken within their hospital admission. This is particularly important for the hospital-acquired sepsis group as patients who have undergone surgical or invasive procedures would be expected to have worse outcomes, including developing sepsis, than those who have not. These issues

of residual confounding mean it is not possible to draw any causal conclusions from the data and more work would be done including the factors mentioned above and any additional unmeasured risk factors to reproduce the findings from these studies.

7.4 Future work

Future work in this area could utilise additional EHR data sources to strengthen the findings in these studies, by reproducing results in different patient populations. It would be important to use a cohort of patients of adults of all ages, to see if there are any differences in outcomes when patients below the age of 65. Other alternative data sources could include the SAIL databank, which contains primary and secondary care data from patients across Wales, along with some critical care and ICNARC audit data. Another source of linked primary and secondary care is the Salford Integrated Record, which covers around 250,000 patients in Greater Manchester. It would be advantageous to have access to a UK based critical care dataset with a level of detail similar to that of MIMIC-III, ideally with linkage to primary care data. This would mean you could follow the same cohort of patients through the patient pathway and could combine information about antibiotic use before and during sepsis. We showed that increased prior use of antibiotics increases the risk of developing sepsis but we did not look at whether that impacts on how patients respond to antibiotics administered during sepsis. With access to microbiological test data it may be possible to see if patients have acquired a resistant strain, and relate that to their prior use and outcomes.

There have been numerous efforts in the last decade or so to provide more data for researchers and to improve the routes of access. Data sources including the Critical Care Health Informatics Collaborative and OpenSafely could be utilised in future, both offer different approaches in terms of the way the data is collected and extracted, with more emphasis on transparency and reproducibility in research.

As well as further work with different data sources there are other analytical methods that could be used. Rather than using a crude measure of antibiotic use the patterns of antibiotic prescriptions could be looked at, for example to see if patients who have regular repeat prescriptions are at greater risk of sepsis.

A potential clinical application for work in this area could be a clinical prediction model to be used by primary care clinicians to predict a patient's risk of sepsis and outcomes when they are having a consultation for a possible infection. It could include a combination of variables around pre-existing comorbidities, clinical observations such as heart rate and blood pressure that can be easily measured by the GP, and variables around previous antibiotic use such as

type, time since last prescription, and number of prescriptions in previous year. By identifying patients at increased risk of sepsis this could help clinicians decide on treatment for an infection and how they manage the patients in terms of monitoring for early signs of sepsis. Not only could this potentially improve the early management and monitoring of infection and reduce the number of people developing sepsis while helping clinicians optimise antibiotic use, which is important in the efforts to reduce their consumption.

In terms of the period after a patient has survived sepsis it would be interesting to investigate appropriateness of prescribing and compare this to before sepsis. The disruption to the gut microbiome and long-term impact of sepsis on the immune system could make sepsis survivors more vulnerable to infection and therefore need treatment with antibiotics. On the other hand, clinicians may prescribe differently in sepsis survivors i.e. more likely to prescribe "just in case" to avoid a secondary sepsis episode.

7.5 Conclusion

This thesis has utilised sources of patient level routinely collected health data from the UK and US to explore the role of antibiotics in patients with sepsis. As well as playing a crucial role in the treatment of sepsis, their use in primary care was shown to be associated with an increased risk of developing sepsis. Additionally, patients who survive a sepsis episode received a greater number of antibiotic prescriptions than they did prior to contracting sepsis. The studies have shown that there are differences between patients who develop sepsis in the community and in hospital.

7.6 References

1. Johnson, A. E. W., Stone, D. J., Celi, L. A. & Pollard, T. J. The MIMIC Code Repository: enabling reproducibility in critical care research. *Journal of the American Medical Informatics Association* **25**, 32–39 (2018).

2. Johnson, A. E. W. *et al.* A Comparative Analysis of Sepsis Identification Methods in an Electronic Database. *Crit Care Med* **46**, 1 (2018).

3. Rezel-Potts, E. *et al.* Sepsis recording in primary care electronic health records, linked hospital episodes and mortality records: Population-based cohort study in England. *PLoS One* **15**, (2020).

4. Herrett, E. *et al.* Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* **44**, 827–836 (2015).

5. Wolf, A. *et al.* Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. *Int J Epidemiol* **48**, 1740-1740G (2019).

Appendices

ISAC protocol

PART 1: APPLICATION FORM

GENERAL INFORMATION ABOUT THE PROPOSED RESEARCH STUDY

1. Study Title (Max. 255 characters)

The evaluation of risk factors and long-term outcomes in patients with community- or hospital- acquired sepsis: a retrospective cohort study using linked primary and secondary care data

2. Research Area (place 'X' in all boxes that apply)

Drug Safety		Economics	
Drug Utilisation		Pharmacoeconomics	
Drug Effectiveness		Pharmacoepidemiology	
Disease Epidemiology	**X**	Methodological	
Health Services Delivery			

3. Chief Investigator

Title:	Professor
Full name:	Tjeerd van Staa
Job title:	Professor in Health e-Research
Affiliation/organisation:	University of Manchester
Email address:	Tjeerd.vanstaa@manchester.ac.uk
CV Number (if applicable):	

4. Corresponding Applicant

Title:	Miss

Full name:	Sian Bladon
Job title:	PhD Student
Affiliation/organisation:	University of Manchester
Email address:	Sian.bladon@postgrad.manchester.ac.uk
CV Number (if applicable):	

5. List of all investigators/collaborators

Title:	Miss
Full name:	Sian Bladon
Job title:	PhD Student
Affiliation/organisation:	University of Manchester
Email address:	Sian.bladon@postgrad.manchester.ac.uk
CV Number (if applicable):	
Will this person be analysing the data? (Y/N)	Y

Title:	Professor
Full name:	Tjeerd van Staa
Job title:	Professor in Health e-Research
Affiliation/organisation:	University of Manchester
Email address:	Tjeerd.vanstaa@ manchester.ac.uk
CV Number (if applicable):	385_15CEL
Will this person be analysing the data? (Y/N)	Y

Title:	Prof
Full name:	Darren Ashcroft
Job title:	Professor of Pharmacoepidemiology
Affiliation/organisation:	University of Manchester
Email address:	Darren.ashcroft@manchester.ac.uk
CV Number (if applicable):	383_15CEPL
Will this person be analysing the data? (Y/N)	N

[Add more investigators/collaborators as necessary by copy and pasting a new table for each investigator/collaborator]

6. Experience/expertise available

List below the member(s) of the research team who have experience with CPRD data.

Name:	**Protocol Number/s:**
Tjeerd van Staa	ISAC 16_153
Darren Ashcroft	ISAC 16_153

List below the member(s) of the research team who have statistical expertise.

Name(s):
Tjeerd van Staa
Sian Bladon

List below the member(s) of the research team who have experience of handling large datasets (greater than 1 million records).

Name(s):
Tjeerd van Staa
Darren Ashcroft

List below the member(s) of the research team, or supporting the research team, who have experience of practicing in UK primary care.

Name(s):

ACCESS TO THE DATA

7. Sponsor of the study

Institution/Organisation:	Centre for Health Informatics - University of Manchester
Address:	Vaughan House Portsmouth Street Manchester M13 9GB

8. Funding source for the study

Same as Sponsor?	Yes		No	X
Institution/Organisation:	National Institute for Health Research - Manchester Biomedical Research Centre – PhD Studentship			
Address:	The Nowgen Centre 29 Grafton Street Manchester M13 9WL			

9. Institution conducting the research

Same as Sponsor?	Yes	X	No	
Institution/Organisation:				
Address:				

10. Data Access Arrangements

Indicate with an '**X**' the method that will be used to access the data for this study:

Study-specific Dataset Agreement	

Institutional Multi-study Licence	X
Institution Name	University of Manchester
Institution Address	Vaughan House Portsmouth Street Manchester

	M13 9GB

Will the dataset be extracted by CPRD?

Yes	X	No	

If yes, provide the reference number: CPRD00035781

11. Data Processor(s):

Processing	X
Accessing	X
Storing	X

Processing area (UK/EEA/Worldwide)	UK
Organisation name	Centre for Health Informatics - University of Manchester
Organisation address	Vaughan House Portsmouth Street Manchester M13 9GB

[Add more processors as necessary by copy and pasting a new table for each processor]

INFORMATION ON DATA

12. Primary care data (place 'X' in all boxes that apply)

CPRD GOLD	X	CPRD Aurum	X

13. Please select any linked data or data products being requested

Patient Level Data (place '**X**' in all boxes that apply)

ONS Death Registration Data	X	CPRD Mother Baby Link	
HES Admitted Patient Care	X	Pregnancy Register	
HES Outpatient		NCRAS (National Cancer Registration and Analysis Service) Cancer Registration Data	
HES Accident and Emergency		NCRAS Cancer Patient Experience Survey (CPES) data	
HES Diagnostic Imaging Dataset		NCRAS Systemic Anti-Cancer Treatment (SACT) data	
HES PROMS (Patient Reported Outcomes Measure)		NCRAS National Radiotherapy Dataset (RTDS) data	
		Mental Health Services Data Set (MHDS)	

Area Level Data (place '**X**' in all boxes that apply)

Practice level (UK)		**Patient level (England only)**	
Practice Level Index of Multiple Deprivation (Standard)		Patient Level Index of Multiple Deprivation	X
Practice Level Index of Multiple Deprivation (Non-standard)		Patient Level Townsend Score	
Practice Level Index of Multiple Deprivation Domains (Non-standard)			
Practice Level Carstairs Index for 2011 Census (Excluding Northern Ireland) (Standard)			
2011 Rural-Urban Classification at LSOA level (Non-standard)			

Reference number (where applicable): CPRD Query 00035781

14. Are you requesting linkage to a dataset not listed above?

Yes		No	**X**

If yes, provide the reference number:

15. Does any person named in this application already have access to any of these data in a patient identifiable form, or associated with an identifiable patient index?

Yes		No	**X**

If yes, provide further details:

VALIDATION/VERIFICATION			
16. Does this protocol describe an observational study using purely CPRD data?			
Yes	**X**	No	
17. Does this protocol involve requesting any additional information from GPs, or contact with patients?			
Yes		No	**X**
If yes, provide the reference number:			

PART TWO: PROTOCOL INFORMATION

Applicants must complete all sections listed below

Sections which do not apply should be completed as 'Not Applicable' and justification provided

A. Study Title (Max. 255 characters)

The evaluation of risk factors and long-term outcomes in patients with community- or hospital-acquired sepsis: a retrospective cohort study using linked primary and secondary care data

B. Lay Summary (Max. 250 words)

Sepsis is caused by an overreaction of a patient's body to an infection. It can result in widespread damage to organs in the body and in some cases can be fatal. Around 250,000 people develop sepsis every year in the UK, causing over 50,000 deaths. There are a number of different factors that make people more or less likely to develop sepsis, including age, gender and whether they already have conditions such as type 2 diabetes or heart disease. Most people develop sepsis in the community, however, there are a number of patients who contract it when they are already in hospital being treated for another condition. The project will use an anonymised dataset of patients in the UK who have a diagnosis of sepsis in their

hospital records. We will access patient's anonymous GP medical records to look at their medical history, including what other health conditions they have and what medications they have been prescribed. The group of sepsis patients will be compared to healthy patients who have not been diagnosed with sepsis. The aim of this project is to understand further the factors associated with developing sepsis, to see if there are differences between patients who develop sepsis in the community and patients who acquire it in hospital. We will assess whether patients receiving more prescriptions of antibiotics from their GP are more likely to develop sepsis. Additionally, we will look at the survival rate of sepsis patients and how many are readmitted to hospital longer term.

C. Technical Summary (Max. 300 words)

Around 250,000 people develop sepsis each year in the UK, with the majority contracting it in the community. It is a complex condition with a wide range of symptoms, making it difficult to recognise clinically. There are many risk factors associated with developing sepsis such as age, gender and multiple comorbidities. Much of the research into sepsis has involved single hospitals or ICU's, with few large population-based cohort studies performed.

The aims of this study are to use linked primary and secondary care data to look at risk factors associated with developing community-acquired and hospital-acquired sepsis, and to see whether increased antibiotic prescribing in primary care increases a patient's risk of developing sepsis. The study will be a retrospective cohort study of patients with a hospital diagnosis of sepsis between 2000 and 2018. Patients diagnosed within 48 hours of admission to hospital will be defined as community-acquired, with those diagnosed more than 48 hours after admission classed as hospital-acquired sepsis. ICD-10 codes for sepsis will be used to extract the cohort in the Hospital Episode Statistics (HES) data and the primary care records obtained from the CPRD GOLD dataset. These will also be linked with Office for National Statistics mortality data. Comparator cohorts of patients without a sepsis diagnosis will be created, matched by age, gender, GP practice or duration of hospital stay prior to index date.

Outcomes assessed will be mortality rates, hospital length of stay, critical care length of stay and readmission rates, comparing the two groups of patients. Survival rates will be compared using Kaplan-Meier plots and modelled using Cox proportional hazards regression. Logistic regression modelling will be used to characterise risk factors for the development of sepsis, including age, gender, comorbidity and prescription data. Analyses will be conducted separately for children (age < 18) and adults.

D. Outcomes to be Measured

In-hospital mortality; admission length of stay; critical care length of stay; all-cause mortality (1-year and longer term); mortality with sepsis as one of the causes of death; all-cause readmission rates (1-year and longer term); readmission with hospital diagnosis of sepsis.

E. Objectives, Specific Aims and Rationale

The overall objective of this study is to use linked primary and secondary care datasets to investigate the risk factors in patients who develop sepsis in the community and in the hospital and assess the differences in outcomes

Specific aims:

(i) To estimate the mortality and readmission rates of sepsis patients in a large population-based cohort

(ii) To estimate differences in outcomes between patients who develop sepsis in the community and those who develop sepsis in the hospital

(iii) To identify differences in risk factors between patients who develop sepsis in the community and those who develop sepsis in the hospital

(iv) To see if increased rates of past antibiotic prescription in primary care increase a patient's risk of developing sepsis

Sepsis is a condition that is the focus of much research, however, there are gaps in the literature. These are discussed further in section F, below. The rationale behind this proposed study, therefore, is to address some of these gaps by using a large population-based cohort of linked primary and secondary care data with longer term follow-up. We will also be differentiating between patients with community-acquired and hospital-acquired sepsis and comparing outcomes between these groups. Patients who contract more infections and receive more antibiotics in the past may be at greater risk of developing sepsis and having worse outcomes due to antimicrobial resistance. A 2010 systematic review and meta-analysis showed that the prescription of antibiotics in primary care is associated with the development of resistance to that antibiotic1. We will therefore be including patient's antibiotic prescription rates in the period prior to their sepsis episode in our analysis to see if this is linked with worse outcomes.

F. Study Background

Sepsis is defined as “life-threatening organ dysfunction caused by a dysregulated host response to infection” 2 and causes around 50,000 deaths in the UK every year 3. There are a number of different risk factors associated with developing sepsis, including age, gender and co-morbidities such as type 2 diabetes, cancer, cardiovascular disease, lung disease and chronic kidney disease 4. Around 85 % of patients develop sepsis in the community with the remainder acquiring it in the hospital. Estimates of mortality rates in the UK are between 20 and 30%, with patients who have hospital-acquired sepsis at higher risk of death 5. Patients who survive a sepsis episode are likely to experience long term health issues as a result of the widespread damage to organs and a reduced quality of life. Due to the high mortality rates and the long-term health implications for patients who survive sepsis it is responsible for high costs to the NHS and social care 6. Recognising sepsis clinically is difficult as many of the symptoms are the same as for a widespread infection. Waiting for test results is not always an option as there is a need to begin treatment as soon as possible. Hourly delays in starting antibiotic treatment in patients with suspected sepsis is associated with worse outcomes 7. Treatment of sepsis consists of an antimicrobial to treat the initial source of infection along with fluid resuscitation, mechanical ventilation and renal replacement therapy 2.

Sepsis is a very heterogeneous disease, patients will experience varying degrees of organ damage and so will present with different symptoms. Patients with more severe sepsis may respond differently to treatment than those with a less severe illness. There are many risk factors associated with sepsis, including a person’s genetic profile. Clinical trials trying to assess the impact of interventions in the treatment of sepsis have often failed because they do not take into account this heterogeneity and treat all patients in the same way 8. There is a need, therefore, to identify different groups within the sepsis population and see who is at greater risk of death. There are some studies that have begun to look at this however they are only focussing on secondary care data, there are none looking at primary care.

Most research looking at sepsis has been conducted in single intensive care units (ICUs) or single hospitals, with limited large population-based cohort studies and no studies using linked primary and secondary care datasets. There have been studies using multiple ICU’s but these will only capture most severely ill patients, not all patients with sepsis will be treated in the ICU 9. A 2017 study used the HES dataset to estimate the number of patients with a suspicion of community-onset sepsis and their outcomes, however their study was limited to hospitals in Oxford over a short time period and they did not link the data to primary care records 10.

A lot of studies focus on the early detection of sepsis in secondary care and predicting patients who are at greater risk of death from sepsis, but they do not address identifying at risk patients in primary care settings 11,12. There have been few studies looking at readmission rates in patients who survive an episode of sepsis. Many studies only look at in-hospital mortality or 90-day mortality rates however this is thought to underestimate the burden of the disease, as more people will die as a result of the longer-term health problems associated with sepsis 13. A study in the US found that more than 20 % of patients who survived a sepsis episode died within 2 years of discharge from a cause not explained by their health status before sepsis. This study only looked at patients with community-acquired sepsis though14.

There are limited studies differentiating between community-acquired and hospital-acquired sepsis and the reported incidences in these vary considerably 15. Hospital-acquired sepsis is usually defined as sepsis diagnosed more than 48 hours after admission to hospital 16. Although it has been found that patients who acquire sepsis in hospital have worse outcomes than those in the community the differences in risk factors prior to admission have not been assessed.

G. Study Type

The study will primarily be descriptive, estimating the mortality and readmission rates in a cohort of patients with sepsis. For aims (ii) and (iii) of the study where we will be identifying differences in outcomes and risk factors between subgroups of the cohort we will be generating hypotheses. Aim (iv) of the study will be testing the hypothesis that increased rates of prescription of antibiotics in primary care increases a patient's risk of developing sepsis.

H. Study Design

The study is a retrospective cohort study. A cohort of patients with a sepsis diagnosis between 2000 and 2018 in the HES dataset will be identified. Patients who have a sepsis diagnosis within 48 hours of the date of hospital admission will be classified as having developed sepsis in the community. Patients who have a sepsis diagnosis in HES greater than 48 hours after the date of hospital admission will be classified as hospital-acquired sepsis. Control groups will be identified for both of these cohort groups. For all of the patients, their GP records will be extracted. The data will also be linked with ONS mortality data.

I. Feasibility counts

A feasibility count requested from CPRD (CPRD00035875, 20/02/2019) indicate there are a total of 61,226 unique patients in the CPRD GOLD linked HES APC dataset with an index data for sepsis diagnosis between 2000 and 2017. These patients are responsible for 116,012 admissions. Table 1 below shows the admission counts stratified by the index year and age group. Given that the ratio of community-acquired to hospital-acquired sepsis is approximately 85:15 it can be estimated that of the 61,226 unique patients 52,042 developed sepsis in the community with the remaining 9,184 contracting it in hospital. The ICD-10 codes used for this feasibility count can be found in Appendix A.

	Count		
Index Year	Adults (> 18)	Children (< 18)	Total
2000	1722	191	1913
2001	2352	175	2527
2002	2925	170	3095
2003	3776	213	3989
2004	4233	187	4420
2005	5058	263	5321
2006	5530	261	5791
2007	5882	297	6179
2008	6118	345	6463
2009	6642	375	7017
2010	7237	358	7595
2011	7767	458	8225
2012	8780	360	9140
2013	8909	481	9390
2014	9108	460	9568
2015	8596	404	9000
2016	7359	343	7702
2017	8396	281	8677

TOTAL110390 5622 116012

Table 1. Estimated number of patients admitted

J. Sample size considerations

Based on a sample size of 61,226 unique sepsis patients, matching on a ratio of 1:6 will give a control cohort of 367,356 patients and a total study sample size of 428,582 patients.

From a previous study using CPRD data around a 1/3 of patients who had received an antibiotic in the previous 3 years was a past user. A conservative estimate of the percentage of patients receiving an antibiotic over a 3-year period is 20 % (Shallcross et al 17 report an estimate of 54 %). Therefore, we have used a prevalence of antibiotic prescription of 0.0666 % over a 3-year period for the power calculations.

Risk Ratio	Expected Power
1.1	99.9 %
1.2	100 %
1.5	100 %
2	100 %
2.5	100 %

Table 2 shows the expected powers to detect changes in RR

Calculations were done using the epi.cohort function in the epiR package in R (version 3.5.1).

K. Planned use of linked data (if applicable):

This study will use CPRD data linked to HES admissions. As sepsis is a condition mainly treated in secondary care the HES data will be used to identify our cohort of sepsis patients and link this back to their GP records to look at their comorbidities and prescriptions prior to

their sepsis episode. ONS mortality data will be used to identify patients who have died after discharge from hospital, either from sepsis or other causes. For patients who survive sepsis their GP records will also be extracted and any readmissions to hospital will be extracted from the HES dataset.

L. Definition of the Study population

Cohort will be identified the HES dataset with the following inclusion criteria:

(i) First ever diagnosis of sepsis in HES during 2000-2018

(ii) The date of hospital admission occurs at least 3 years after the start of data collection in the CPRD general practice (i.e., latest of registration date and start of data collection) with the exception of younger children

(iii) Patients of any age alive and registered in the CPRD practice and alive prior to the date of hospital admission

(iv) Patients will be excluded if there was a sepsis records in the primary care records six weeks prior or earlier (in order to identify first ever sepsis). Sepsis that occur in the 6-week period immediately prior to the hospital admission for sepsis will be considered part of the developing sepsis.

The index date will be the date of diagnosis of sepsis. Patients will remain in the cohort until their date of death, date of leaving the practice or end of CPRD data collection (whatever date came earliest).

M. Selection of comparison group(s) or controls

For the community-acquired sepsis cohort there will be a population-based control with patients who will be matched by calendar time, age (stepwise within 5 years), gender and GP practice (if no control can be found with 5 years of age, controls will be selected from other practices). Controls with a hospital admission in the 3 months prior to the index date will be excluded from the study.

For the hospital-acquired sepsis cohort the control group will be patients admitted to hospital with a non-infectious diagnosis. They will be matched by calendar time (within 3 months), age (stepwise within 5 years), gender, and duration of hospital length of stay prior to the index date (stepwise within 5 days).

Matching will be done on a ratio of 1:6.

N. Exposures, Outcomes and Covariates

Exposures: in-hospital diagnosis of sepsis in the HES dataset, using ICD-10 codes (see Appendix A). We will differentiate between patients with community- and hospital- acquired sepsis by looking at the time stamp of the diagnosis. Patients diagnosed within 48 hours of admission will be defined as cases of community-acquired sepsis whereas those diagnosed after this 48-hour period will be defined as cases of hospital-acquired sepsis.

Outcomes: in-hospital mortality from the HES dataset, readmission, hospital length of stay, critical care length of stay, and post discharge mortality taken from the ONS datasets

Covariates:

(i) primary records: age, gender, ethnicity, smoking status, body mass index, comorbidities (including Charlson co-morbidity score, see Appendix B for Read code list), prior prescribing and number of GP consultations in the 6 to 18 weeks before (including the Charlson prescription score), number and type of antibiotic prescribed in the 6 to 162 weeks before (a three year period excluding the time immediate prior to the date of sepsis) and use of antibiotic and GP consultations in 30 days prior to diagnosis.

(ii) HES records: ethnicity, diagnoses and surgeries prior to the date of sepsis,

(iii) IMD socioeconomic status.

The code lists will be based on the previously approved BRIT study evaluating antibiotics use and common infection in primary care (ISAC 16_153).

O. Data/ Statistical Analysis

Analysis for aim (i) will include baseline summary statistics of the sepsis cohort, calculating the mean or median for each variable. Differences between the sub-cohorts of community- and hospital- acquired sepsis patients will be assessed using appropriate univariate comparisons for continuous (e.g. Student's t-test) and categorical variables (e.g. Chi Square test). All-cause mortality and readmission rates will be calculated.

For aim (ii) of the study Kaplan-Meier survival plots will be generated stratifying by age, gender, community-acquired vs hospital acquired sepsis and other key covariates. Log-rank tests will be used to test if there are any significant differences between the groups. Further longitudinal time-to-event analysis will be done using Cox proportional hazards regression with censoring of patients in case of end of registration of data collection. The proportionality of hazards rates will be evaluated as the effects of sepsis on the outcomes may vary over time.

To address aim (iii) logistic regression will be performed to evaluate the predictors prior to the index date. Development of sepsis will be the outcome used with separate models for the community-acquired and hospital-acquired cohorts. We will select variables to be included in the models using a stepwise method and will estimate odds ratios and 95% confidence intervals for variables in the final model. Multivariate regression will be used to reduce the effects of confounding.

For aim (iv) the percentage of patients who have received an antibiotic prescription in the 3 years prior to the index date will be calculated and compared between the sepsis and control groups. A risk ratio will be calculated to see if exposure to antibiotics increases a person's risk of developing sepsis. The antibiotic prescription rate for each patient over the 3-year period will be calculated and included in the multivariable logistic regression models as a potential predictor of developing sepsis, to assess whether increases in prescription rate increases a patient's odds of developing sepsis.

P. Plan for addressing confounding

Regression analyses will be used to minimise confounding by measured confounders. Although we will be unable to address unmeasured confounding, we will discuss our findings with sepsis clinical experts (Professor Dark and Dr Tim Felton) and GP (Dr Benjamin Brown) and Pharmacist (Prof Darren Ashcroft) to identify any major sources of unmeasured confounding and substantive limitations of this work.

Q. Plans for addressing missing data

There will be missing data for some of the risk factors such as body mass index and smoking history. We will use multiple imputation to estimate values for missing values.

R. Patient or user group involvement (if applicable)

We will discuss our results with the patient engagement group of the Biomedical Research Centre (Sian Bladon is funded by this centre). We will also with work with Professor Paul Dark and Dr Tim Felton, ICU consultants, who have established contacts with patients groups of patients who suffered sepsis.

S. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

The results from this study will form part of Sian Bladon's PhD thesis. They will also be published in peer-reviewed academic journals and presented at conferences in an oral or poster format.

Conflict of interest statement:

The applicant and investigators declare no conflict of interest. Sian Bladon receives PhD funding through the NIHR Manchester Biomedical Research Centre.

T. Limitations of the study design, data sources, and analytic methods

Extraction of the cohort will be done by ICD-10 codes only, which has been shown to underestimate or overestimate the sepsis population depending on the method used 18. The HES dataset has limited secondary care data and we will not be able to look at levels of organ dysfunction experienced by the patients. CPRD only covers around 8 % of the UK population so the results may not be generalisable to the whole of the UK.

U. References

1. Costelloe, C., Metcalfe, C., Lovering, A., Mant, D. & Hay, A. D. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. Bmj 340, c2096–c2096 (2010).

2. Singer, M. et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 315, 801 (2016).

3. Daniels, R. et al. The Sepsis Manual. (United Kingdom Sepsis Trust, 2017).

4. Tavaré, A. & O'Flynn, N. Recognition, diagnosis, and early management of sepsis: NICE guideline. Br. J. Gen. Pract. 67, 185–186 (2017).

5. Jones, S. L. et al. Outcomes and resource use of sepsis-associated stays by presence on admission, severity, and hospital type. Med. Care 54, 303–310 (2016).

6. Schmidt, K. et al. Sepsis survivors monitoring and coordination in outpatient health care (SMOOTH): study protocol for a randomized controlled trial. Trials 15, 283 (2014).

7. Ferrer, R. et al. Empiric Antibiotic Treatment Reduces Mortality in Severe Sepsis and Septic Shock From the First Hour: Results From a Guideline-Based Performance Improvement Program*. (2014). doi:10.1097/CCM.0000000000000330

8. Marshall, J. C. Why have clinical trials in sepsis failed? Trends Mol. Med. 20, 195–203 (2014).

9. Sakr, Y. et al. Sepsis in Intensive Care Unit Patients: Worldwide data from the ICON audit. Open Forum Infect. Dis. (2018). doi:10.1093/ofid/ofy313

10. Inada-Kim, M., Page, B., Maqsood, I. & Vincent, C. Defining and measuring suspicion of sepsis: An analysis of routine data. BMJ Open 7, (2017).

11. Shashikumar, S. P. et al. Early sepsis detection in critical care patients using multiscale blood pressure and heart rate dynamics. J. Electrocardiol. 50, 739–743 (2017).

12. Calvert, J. S. et al. A computational approach to early sepsis detection. Comput. Biol. Med. 74, 69–73 (2016).

13. Winters, B. D. et al. Long-term mortality and quality of life in sepsis: A systematic review. Crit. Care Med. 38, 1276–1283 (2010).

14. Prescott, H. C., Osterholzer, J. J., Langa, K. M., Angus, D. C. & Iwashyna, T. J. Late mortality after sepsis: propensity matched cohort study. BMJ 353, i2375 (2016).

15. Tsertsvadze, A. et al. Community-onset sepsis and its public health burden: A systematic review. Syst. Rev. 5, (2016).

16. Sousa, C., Brandão, M., Ribeiro, O. & Cardoso, T. Community-Acquired Severe Sepsis: A Prospective Cohort Study. Open J. Intern. Med. 05, 37–49 (2015).

17. Shallcross, L., Beckley, N., Rait, G., Hayward, A. & Petersen, I. Antibiotic prescribing frequency amongst patients in primary care: a cohort study using electronic health records. J. Antimicrob. Chemother. 72, 1818–1824 (2017).

18. Fleischmann-Struzek, C. et al. Comparing the validity of different ICD coding abstraction strategies for sepsis case identification in German claims data. PLoS One 13, e0198847 (2018).

Code lists

ICD-10 codes for sepsis admissions

ICD-10 CODE	CODE TITLE
A021	Salmonella sepsis
A207	Septicaemic plague
A227	Anthrax sepsis
A267	Erysipelothrix sepsis
A327	Listerial sepsis
A392	Acute meningococcaemia
A393	Chronic meningococcaemia
A394	Meningococcaemia, unspecified
A400	Sepsis due to streptococcus, group A
A401	Sepsis due to streptococcus, group B
A402	Sepsis due to streptococcus, group D
A403	Sepsis due to Streptococcus pneumoniae
A408	Other streptococcal sepsis
A409	Streptococcal sepsis, unspecified
A410	Sepsis due to Staphylococcus aureus
A411	Sepsis due to other specified staphylococcus
A412	Sepsis due to unspecified staphylococcus
A413	Sepsis due to Haemophilus influenzae
A414	Sepsis due to anaerobes
A415	Sepsis due to other Gram-negative organisms
A418	Other specified sepsis
A419	Sepsis, unspecified
A427	Actinomycotic sepsis
B007	Disseminated herpesviral disease
O85X	Puerperal sepsis
P360	Sepsis of newborn due to streptococcus, group B
P361	Sepsis of newborn due to other and unspecified streptococci
P362	Sepsis of newborn due to Staphylococcus aureus
P363	Sepsis of newborn due to other and unspecified staphylococci
P364	Sepsis of newborn due to Escherichia coli
P365	Sepsis of newborn due to anaerobes
P368	Other bacteiral spesis of newborn
P369	Bacterial sepsis of newborn, unspecified
R572	Septic shock
R651	Systemic Inflammatory Response Syndrome of infectious origin with organ failure

Read and Medcodes for Charlson comorbidities

medcoRde	read_code	description
10335	1O0..00	Cancer confirmed
52946	4C53.00	Bone marrow: myeloma cells
65172	4C54.00	Bone marrow: tumour cells
49341	4D56.00	Pleural fluid: malignant cells
59076	4E33.00	Sputum: malignant cells
13575	4F32.00	Ascitic fluid: malignant cells
7728	4K24.00	Cerv.smear: severe dyskaryosis
223	4K24.11	CIN III - severe dyskaryosis
5276	4K25.00	Cerv.smear:severe dysk.?inv.ca
107264	4K2L.00	Cervical smear - high grade dyskaryosis (severe)
107456	4K2M.00	Crv smr - hi grade dyskaryosis? invasive squamous carcinoma
23224	4M...00	Tumour staging
10178	4M0..00	Gleason grading of prostate cancer
18503	4M00.00	Gleason prostate grade 2-4 (low)
18612	4M01.00	Gleason prostate grade 5-7 (medium)
26081	4M02.00	Gleason prostate grade 8-10 (high)
12033	4M1..00	Dukes staging system
40986	4M10.00	Dukes stage A
19092	4M11.00	Dukes stage B
35458	4M12.00	Dukes stage C1
42361	4M13.00	Dukes stage C2
64727	4M14.00	Dukes stage D
40991	4M2..00	Lymphoma staging system
60918	4M20.00	Lymphoma stage I
94935	4M21.00	Lymphoma stage II
32240	4M22.00	Lymphoma stage III
71672	4M23.00	Lymphoma stage IV
57294	4M3..00	Breslow depth staging for melanoma
37793	4M4..00	FIGO staging of gynaecological malignancy
57122	4M5..00	TNM tumour staging
94688	4M6..00	Recurrence of tumour
97188	4M7..00	Clark staging levels
101198	4M70.00	Clark melanoma level 1
104609	4M71.00	Clark melanoma level 2
96280	4M72.00	Clark melanoma level 3
102116	4M73.00	Clark melanoma level 4
108866	4M74.00	Clark melanoma level 5
108905	68W2400	Bowel scope (flexible sigmoidoscopy) screen: cancer detected
94000	9Ow1.00	Bowel cancer detected by national screening programme
67575	A788W00	HIV disease resulting in unspecified malignant neoplasm
44617	A789600	HIV disease resulting in Burkitt's lymphoma
66367	A789700	HIV dis resulting oth types of non-Hodgkin's lymphoma
105324	A789800	HIV disease resulting in multiple malignant neoplasms
51708	A789X00	HIV dis reslt/oth mal neopl/lymph,h'matopoetc+reltd tissu
69767	AyuC600	[X]HIV disease resulting in other non-Hodgkin's lymphoma
2755	B....11	Cancers
19415	B0...00	Malignant neoplasm of lip, oral cavity and pharynx
24374	B0...11	Carcinoma of lip, oral cavity and pharynx
14712	B00..00	Malignant neoplasm of lip

9984	B00..11	Carcinoma of lip
73962	B000.00	Malignant neoplasm of upper lip, vermilion border
66270	B000000	Malignant neoplasm of upper lip, external
50296	B000100	Malignant neoplasm of upper lip, lipstick area
98740	B000z00	Malignant neoplasm of upper lip, vermilion border NOS
67446	B001.00	Malignant neoplasm of lower lip, vermilion border
66384	B001000	Malignant neoplasm of lower lip, external
95480	B001100	Malignant neoplasm of lower lip, lipstick area
101707	B001z00	Malignant neoplasm of lower lip, vermilion border NOS
99493	B002.00	Malignant neoplasm of upper lip, inner aspect
99001	B002100	Malignant neoplasm of upper lip, frenulum
98500	B002200	Malignant neoplasm of upper lip, mucosa
90610	B002300	Malignant neoplasm of upper lip, oral aspect
100721	B002z00	Malignant neoplasm of upper lip, inner aspect NOS
71147	B003.00	Malignant neoplasm of lower lip, inner aspect
67504	B003000	Malignant neoplasm of lower lip, buccal aspect
91843	B003100	Malignant neoplasm of lower lip, frenulum
89909	B003200	Malignant neoplasm of lower lip, mucosa
94441	B003300	Malignant neoplasm of lower lip, oral aspect
96782	B003z00	Malignant neoplasm of lower lip, inner aspect NOS
61692	B004.00	Malignant neoplasm of lip unspecified, inner aspect
73614	B004000	Malignant neoplasm of lip unspecified, buccal aspect
68399	B004200	Malignant neoplasm of lip unspecified, mucosa
100144	B004300	Malignant neoplasm of lip, oral aspect
96783	B005.00	Malignant neoplasm of commissure of lip
18882	B006.00	Malignant neoplasm of overlapping lesion of lip
37553	B007.00	Malignant neoplasm of lip, unspecified
100906	B00z000	Malignant neoplasm of lip, unspecified, external
94251	B00z100	Malignant neoplasm of lip, unspecified, lipstick area
69761	B00zz00	Malignant neoplasm of lip, vermilion border NOS
10283	B01..00	Malignant neoplasm of tongue
43431	B010.00	Malignant neoplasm of base of tongue
69671	B010.11	Malignant neoplasm of posterior third of tongue
34409	B010000	Malignant neoplasm of base of tongue dorsal surface
91035	B010z00	Malignant neoplasm of fixed part of tongue NOS
43642	B011.00	Malignant neoplasm of dorsal surface of tongue
107258	B011100	Malignant neoplasm of midline of tongue
43781	B011z00	Malignant neoplasm of dorsum of tongue NOS
36161	B012.00	Malignant neoplasm of tongue, tip and lateral border
62840	B013.00	Malignant neoplasm of ventral surface of tongue
102142	B013000	Malignant neoplasm of anterior 2/3 of tongue ventral surface
63979	B013100	Malignant neoplasm of frenulum linguae
38488	B013z00	Malignant neoplasm of ventral tongue surface NOS
58121	B014.00	Malignant neoplasm of anterior 2/3 of tongue unspecified
37096	B015.00	Malignant neoplasm of tongue, junctional zone
24852	B016.00	Malignant neoplasm of lingual tonsil

47205	B017.00	Malignant overlapping lesion of tongue
41530	B01y.00	Malignant neoplasm of other sites of tongue
40557	B01z.00	Malignant neoplasm of tongue NOS
20292	B02..00	Malignant neoplasm of major salivary glands
4388	B020.00	Malignant neoplasm of parotid gland
51786	B021.00	Malignant neoplasm of submandibular gland
70928	B022.00	Malignant neoplasm of sublingual gland
70696	B02y.00	Malignant neoplasm of other major salivary glands
50475	B02z.00	Malignant neoplasm of major salivary gland NOS
43400	B03..00	Malignant neoplasm of gum
32024	B030.00	Malignant neoplasm of upper gum
49360	B031.00	Malignant neoplasm of lower gum
101753	B03y.00	Malignant neoplasm of other sites of gum
93218	B03z.00	Malignant neoplasm of gum NOS
20092	B04..00	Malignant neoplasm of floor of mouth
45408	B040.00	Malignant neoplasm of anterior portion of floor of mouth
45986	B041.00	Malignant neoplasm of lateral portion of floor of mouth
17912	B042.00	Malignant neoplasm, overlapping lesion of floor of mouth
56709	B04y.00	Malignant neoplasm of other sites of floor of mouth
36716	B04z.00	Malignant neoplasm of floor of mouth NOS
14792	B05..00	Malignant neoplasm of other and unspecified parts of mouth
31364	B050.00	Malignant neoplasm of cheek mucosa
30402	B050.11	Malignant neoplasm of buccal mucosa
103796	B051.00	Malignant neoplasm of vestibule of mouth
95772	B051000	Malignant neoplasm of upper buccal sulcus
97530	B051100	Malignant neoplasm of lower buccal sulcus
37590	B052.00	Malignant neoplasm of hard palate
40292	B053.00	Malignant neoplasm of soft palate
37516	B054.00	Malignant neoplasm of uvula
70819	B055.00	Malignant neoplasm of palate unspecified
96003	B055000	Malignant neoplasm of junction of hard and soft palate
69951	B055100	Malignant neoplasm of roof of mouth
28559	B055z00	Malignant neoplasm of palate NOS
37724	B056.00	Malignant neoplasm of retromolar area
37916	B05y.00	Malignant neoplasm of other specified mouth parts
55015	B05z.00	Malignant neoplasm of mouth NOS
37549	B05z000	Kaposi's sarcoma of palate
22893	B06..00	Malignant neoplasm of oropharynx
16241	B060.00	Malignant neoplasm of tonsil
26448	B060000	Malignant neoplasm of faucial tonsil
101988	B060100	Malignant neoplasm of palatine tonsil
102151	B060200	Malignant neoplasm of overlapping lesion of tonsil
53884	B060z00	Malignant neoplasm tonsil NOS
24397	B061.00	Malignant neoplasm of tonsillar fossa
55066	B062.00	Malignant neoplasm of tonsillar pillar
51926	B062000	Malignant neoplasm of faucial pillar

99185	B062100	Malignant neoplasm of glossopalatine fold
61510	B062200	Malignant neoplasm of palatoglossal arch
93842	B062300	Malignant neoplasm of palatopharyngeal arch
100002	B062z00	Malignant neoplasm of tonsillar fossa NOS
39554	B063.00	Malignant neoplasm of vallecula
46728	B064.00	Malignant neoplasm of anterior epiglottis
26134	B064000	Malignant neoplasm of epiglottis, free border
91895	B064100	Malignant neoplasm of glossoepiglottic fold
73439	B064z00	Malignant neoplasm of anterior epiglottis NOS
48519	B065.00	Malignant neoplasm of junctional region of epiglottis
56355	B066.00	Malignant neoplasm of lateral wall of oropharynx
90124	B067.00	Malignant neoplasm of posterior wall of oropharynx
67323	B06y.00	Malignant neoplasm of oropharynx, other specified sites
91037	B06yz00	Malignant neoplasm of other specified site of oropharynx NOS
43200	B06z.00	Malignant neoplasm of oropharynx NOS
24675	B07..00	Malignant neoplasm of nasopharynx
94390	B070.00	Malignant neoplasm of roof of nasopharynx
95429	B071.00	Malignant neoplasm of posterior wall of nasopharynx
33388	B071000	Malignant neoplasm of adenoid
46548	B071100	Malignant neoplasm of pharyngeal tonsil
96869	B071z00	Malignant neoplasm of posterior wall of nasopharynx NOS
59004	B072.00	Malignant neoplasm of lateral wall of nasopharynx
37940	B072000	Malignant neoplasm of pharyngeal recess
102205	B072z00	Malignant neoplasm of lateral wall of nasopharynx NOS
44139	B073.00	Malignant neoplasm of anterior wall of nasopharynx
106915	B073100	Malignant neoplasm of nasopharyngeal soft palate surface
99386	B073200	Malignant neoplasm posterior margin nasal septum and choanae
100918	B073z00	Malignant neoplasm of anterior wall of nasopharynx NOS
66422	B074.00	Malignant neoplasm, overlapping lesion of nasopharynx
55630	B07y.00	Malignant neoplasm of other specified site of nasopharynx
28665	B07z.00	Malignant neoplasm of nasopharynx NOS
34012	B08..00	Malignant neoplasm of hypopharynx
43548	B080.00	Malignant neoplasm of postcricoid region
39897	B081.00	Malignant neoplasm of pyriform sinus
57248	B082.00	Malignant neoplasm aryepiglottic fold, hypopharyngeal aspect
64462	B083.00	Malignant neoplasm of posterior pharynx
88362	B08y.00	Malignant neoplasm of other specified hypopharyngeal site
28451	B08z.00	Malignant neoplasm of hypopharynx NOS
46114	B0z..00	Malig neop other/ill-defined sites lip, oral cavity, pharynx
16297	B0z0.00	Malignant neoplasm of pharynx unspecified
95016	B0z1.00	Malignant neoplasm of Waldeyer's ring
39084	B0z2.00	Malignant neoplasm of laryngopharynx
49758	B0zy.00	Malignant neoplasm of other sites lip, oral cavity, pharynx
39430	B0zz.00	Malignant neoplasm of lip, oral cavity and pharynx NOS
15709	B1...00	Malignant neoplasm of digestive organs and peritoneum
3357	B1...11	Carcinoma of digestive organs and peritoneum

1062	B10..00	Malignant neoplasm of oesophagus
61695	B100.00	Malignant neoplasm of cervical oesophagus
41362	B101.00	Malignant neoplasm of thoracic oesophagus
63470	B102.00	Malignant neoplasm of abdominal oesophagus
50789	B103.00	Malignant neoplasm of upper third of oesophagus
54171	B104.00	Malignant neoplasm of middle third of oesophagus
42416	B105.00	Malignant neoplasm of lower third of oesophagus
67497	B106.00	Malignant neoplasm, overlapping lesion of oesophagus
98142	B107.00	Siewert type I adenocarcinoma
53591	B10y.00	Malignant neoplasm of other specified part of oesophagus
30700	B10z.00	Malignant neoplasm of oesophagus NOS
4865	B10z.11	Oesophageal cancer
8386	B11..00	Malignant neoplasm of stomach
32022	B110.00	Malignant neoplasm of cardia of stomach
100584	B110000	Malignant neoplasm of cardiac orifice of stomach
22894	B110100	Malignant neoplasm of cardio-oesophageal junction of stomach
94278	B110111	Malignant neoplasm of gastro-oesophageal junction
37859	B110z00	Malignant neoplasm of cardia of stomach NOS
21620	B111.00	Malignant neoplasm of pylorus of stomach
48237	B111000	Malignant neoplasm of prepylorus of stomach
41215	B111100	Malignant neoplasm of pyloric canal of stomach
59092	B111z00	Malignant neoplasm of pylorus of stomach NOS
19318	B112.00	Malignant neoplasm of pyloric antrum of stomach
32362	B113.00	Malignant neoplasm of fundus of stomach
43572	B114.00	Malignant neoplasm of body of stomach
42193	B115.00	Malignant neoplasm of lesser curve of stomach unspecified
55434	B116.00	Malignant neoplasm of greater curve of stomach unspecified
51690	B117.00	Malignant neoplasm, overlapping lesion of stomach
97499	B118.00	Siewert type II adenocarcinoma
96094	B119.00	Siewert type III adenocarcinoma
55019	B11y.00	Malignant neoplasm of other specified site of stomach
65312	B11y000	Malignant neoplasm of anterior wall of stomach NEC
96802	B11y100	Malignant neoplasm of posterior wall of stomach NEC
65372	B11yz00	Malignant neoplasm of other specified site of stomach NOS
14800	B11z.00	Malignant neoplasm of stomach NOS
6806	B12..00	Malignant neoplasm of small intestine and duodenum
18613	B120.00	Malignant neoplasm of duodenum
43479	B121.00	Malignant neoplasm of jejunum
33871	B122.00	Malignant neoplasm of ileum
63995	B123.00	Malignant neoplasm of Meckel's diverticulum
66166	B124.00	Malignant neoplasm, overlapping lesion of small intestine
99896	B12y.00	Malignant neoplasm of other specified site small intestine
43390	B12z.00	Malignant neoplasm of small intestine NOS
1220	B13..00	Malignant neoplasm of colon
9088	B130.00	Malignant neoplasm of hepatic flexure of colon
6935	B131.00	Malignant neoplasm of transverse colon

10864	B132.00	Malignant neoplasm of descending colon
2815	B133.00	Malignant neoplasm of sigmoid colon
3811	B134.00	Malignant neoplasm of caecum
22163	B134.11	Carcinoma of caecum
18632	B135.00	Malignant neoplasm of appendix
10946	B136.00	Malignant neoplasm of ascending colon
18619	B137.00	Malignant neoplasm of splenic flexure of colon
93478	B138.00	Malignant neoplasm, overlapping lesion of colon
101700	B139.00	Hereditary nonpolyposis colon cancer
48231	B13y.00	Malignant neoplasm of other specified sites of colon
28163	B13z.00	Malignant neoplasm of colon NOS
9118	B13z.11	Colonic cancer
35357	B14..00	Malignant neoplasm of rectum, rectosigmoid junction and anus
27855	B140.00	Malignant neoplasm of rectosigmoid junction
1800	B141.00	Malignant neoplasm of rectum
7219	B141.11	Carcinoma of rectum
5901	B141.12	Rectal carcinoma
24370	B142.00	Malignant neoplasm of anal canal
9491	B142.11	Anal carcinoma
46159	B142000	Malignant neoplasm of cloacogenic zone
27897	B143.00	Malignant neoplasm of anus unspecified
55659	B14y.00	Malig neop other site rectum, rectosigmoid junction and anus
50974	B14z.00	Malignant neoplasm rectum,rectosigmoid junction and anus NOS
8918	B15..00	Malignant neoplasm of liver and intrahepatic bile ducts
25535	B150.00	Primary malignant neoplasm of liver
16126	B150000	Primary carcinoma of liver
31210	B150100	Hepatoblastoma of liver
68410	B150200	Primary angiosarcoma of liver
22187	B150300	Hepatocellular carcinoma
44399	B150z00	Primary malignant neoplasm of liver NOS
16915	B151.00	Malignant neoplasm of intrahepatic bile ducts
65124	B151000	Malignant neoplasm of interlobular bile ducts
89593	B151200	Malignant neoplasm of intrahepatic biliary passages
58088	B151400	Malignant neoplasm of intrahepatic gall duct
61643	B151z00	Malignant neoplasm of intrahepatic bile ducts NOS
26393	B152.00	Malignant neoplasm of liver unspecified
38978	B15z.00	Malignant neoplasm of liver and intrahepatic bile ducts NOS
54103	B16..00	Malignant neoplasm gallbladder and extrahepatic bile ducts
16105	B160.00	Malignant neoplasm of gallbladder
31393	B160.11	Carcinoma gallbladder
23433	B161.00	Malignant neoplasm of extrahepatic bile ducts
72445	B161000	Malignant neoplasm of cystic duct
52537	B161100	Malignant neoplasm of hepatic duct
7982	B161200	Malignant neoplasm of common bile duct
36495	B161211	Carcinoma common bile duct
105613	B161300	Malignant neoplasm of sphincter of Oddi

74896	B161z00	Malignant neoplasm of extrahepatic bile ducts NOS
10949	B162.00	Malignant neoplasm of ampulla of Vater
35039	B163.00	Malignant neoplasm, overlapping lesion of biliary tract
60312	B16y.00	Malignant neoplasm other gallbladder/extrahepatic bile duct
15907	B16z.00	Malignant neoplasm gallbladder/extrahepatic bile ducts NOS
8166	B17..00	Malignant neoplasm of pancreas
8771	B170.00	Malignant neoplasm of head of pancreas
40810	B171.00	Malignant neoplasm of body of pancreas
39870	B172.00	Malignant neoplasm of tail of pancreas
35535	B173.00	Malignant neoplasm of pancreatic duct
35795	B174.00	Malignant neoplasm of Islets of Langerhans
97875	B175.00	Malignant neoplasm, overlapping lesion of pancreas
48537	B17y.00	Malignant neoplasm of other specified sites of pancreas
96635	B17y000	Malignant neoplasm of ectopic pancreatic tissue
95783	B17yz00	Malignant neoplasm of specified site of pancreas NOS
34388	B17z.00	Malignant neoplasm of pancreas NOS
44108	B18..00	Malignant neoplasm of retroperitoneum and peritoneum
21330	B180.00	Malignant neoplasm of retroperitoneum
65159	B180100	Malignant neoplasm of perinephric tissue
24048	B180200	Malignant neoplasm of retrocaecal tissue
61555	B180z00	Malignant neoplasm of retroperitoneum NOS
17874	B181.00	Mesothelioma of peritoneum
101907	B182.00	Overlapping malign lesion of retroperitoneum and peritoneum
46613	B18y.00	Malignant neoplasm of specified parts of peritoneum
59388	B18y100	Malignant neoplasm of mesocaecum
30165	B18y200	Malignant neoplasm of mesorectum
50898	B18y300	Malignant neoplasm of omentum
64516	B18y400	Malignant neoplasm of parietal peritoneum
39413	B18y500	Malignant neoplasm of pelvic peritoneum
69821	B18y600	Malignant neoplasm of the pouch of Douglas
90290	B18y700	Malignant neoplasm of mesentery
64106	B18yz00	Malignant neoplasm of specified parts of peritoneum NOS
16298	B18z.00	Malignant neoplasm of retroperitoneum and peritoneum NOS
11009	B1z..00	Malig neop oth/ill-defined sites digestive tract/peritoneum
17559	B1z0.00	Malignant neoplasm of intestinal tract, part unspecified
11628	B1z0.11	Cancer of bowel
65460	B1z1.00	Malignant neoplasm of spleen NEC
108667	B1z1000	Angiosarcoma of spleen
72224	B1z1100	Fibrosarcoma of spleen
93778	B1z1z00	Malignant neoplasm of spleen NOS
94776	B1z2.00	Malignant neoplasm, overlapping lesion of digestive system
56918	B1zy.00	Malignant neoplasm other spec digestive tract and peritoneum
51255	B1zz.00	Malignant neoplasm of digestive tract and peritoneum NOS
34075	B2...00	Malig neop of respiratory tract and intrathoracic organs
45307	B2...11	Carcinoma of respiratory tract and intrathoracic organs
26652	B20..00	Malig neop nasal cavities, middle ear and accessory sinuses

23389	B200.00	Malignant neoplasm of nasal cavities
71204	B200000	Malignant neoplasm of cartilage of nose
98911	B200100	Malignant neoplasm of nasal conchae
62761	B200200	Malignant neoplasm of septum of nose
62182	B200300	Malignant neoplasm of vestibule of nose
42856	B200z00	Malignant neoplasm of nasal cavities NOS
24456	B201.00	Malig neop auditory tube, middle ear and mastoid air cells
107916	B201000	Malignant neoplasm of auditory (Eustachian) tube
98537	B201100	Malignant neoplasm of tympanic cavity
54613	B201200	Malignant neoplasm of tympanic antrum
71946	B201300	Malignant neoplasm of mastoid air cells
73537	B201z00	Malig neop auditory tube, middle ear, mastoid air cells NOS
32174	B202.00	Malignant neoplasm of maxillary sinus
54636	B203.00	Malignant neoplasm of ethmoid sinus
15684	B204.00	Malignant neoplasm of frontal sinus
65215	B205.00	Malignant neoplasm of sphenoidal sinus
39590	B206.00	Malignant neoplasm, overlapping lesion of accessory sinuses
96971	B20y.00	Malig neop other site nasal cavity, middle ear and sinuses
55246	B20z.00	Malignant neoplasm of accessory sinus NOS
319	B21..00	Malignant neoplasm of larynx
318	B210.00	Malignant neoplasm of glottis
26165	B211.00	Malignant neoplasm of supraglottis
22441	B212.00	Malignant neoplasm of subglottis
43111	B213.00	Malignant neoplasm of laryngeal cartilage
63460	B213000	Malignant neoplasm of arytenoid cartilage
37805	B213100	Malignant neoplasm of cricoid cartilage
107878	B213200	Malignant neoplasm of cuneiform cartilage
47862	B213300	Malignant neoplasm of thyroid cartilage
97332	B213z00	Malignant neoplasm of laryngeal cartilage NOS
50579	B214.00	Malignant neoplasm, overlapping lesion of larynx
55374	B215.00	Malignant neoplasm of epiglottis NOS
26813	B21y.00	Malignant neoplasm of larynx, other specified site
9237	B21z.00	Malignant neoplasm of larynx NOS
13243	B22..00	Malignant neoplasm of trachea, bronchus and lung
15221	B220.00	Malignant neoplasm of trachea
103946	B220100	Malignant neoplasm of mucosa of trachea
37810	B220z00	Malignant neoplasm of trachea NOS
12870	B221.00	Malignant neoplasm of main bronchus
17391	B221000	Malignant neoplasm of carina of bronchus
33444	B221100	Malignant neoplasm of hilus of lung
21698	B221z00	Malignant neoplasm of main bronchus NOS
10358	B222.00	Malignant neoplasm of upper lobe, bronchus or lung
20170	B222.11	Pancoast's syndrome
31700	B222000	Malignant neoplasm of upper lobe bronchus
25886	B222100	Malignant neoplasm of upper lobe of lung
44169	B222z00	Malignant neoplasm of upper lobe, bronchus or lung NOS

31268	B223.00	Malignant neoplasm of middle lobe, bronchus or lung
41523	B223000	Malignant neoplasm of middle lobe bronchus
39923	B223100	Malignant neoplasm of middle lobe of lung
54134	B223z00	Malignant neoplasm of middle lobe, bronchus or lung NOS
31188	B224.00	Malignant neoplasm of lower lobe, bronchus or lung
18678	B224000	Malignant neoplasm of lower lobe bronchus
12582	B224100	Malignant neoplasm of lower lobe of lung
42566	B224z00	Malignant neoplasm of lower lobe, bronchus or lung NOS
36371	B225.00	Malignant neoplasm of overlapping lesion of bronchus & lung
7484	B226.00	Mesothelioma
38961	B22y.00	Malignant neoplasm of other sites of bronchus or lung
3903	B22z.00	Malignant neoplasm of bronchus or lung NOS
2587	B22z.11	Lung cancer
31573	B23..00	Malignant neoplasm of pleura
67107	B230.00	Malignant neoplasm of parietal pleura
106194	B231.00	Malignant neoplasm of visceral pleura
9600	B232.00	Mesothelioma of pleura
98104	B23y.00	Malignant neoplasm of other specified pleura
34742	B23z.00	Malignant neoplasm of pleura NOS
62556	B24..00	Malignant neoplasm of thymus, heart and mediastinum
27483	B240.00	Malignant neoplasm of thymus
95644	B241.00	Malignant neoplasm of heart
63430	B241000	Malignant neoplasm of endocardium
65605	B241200	Malignant neoplasm of myocardium
94975	B241300	Malignant neoplasm of pericardium
101885	B241400	Mesothelioma of pericardium
50289	B241z00	Malignant neoplasm of heart NOS
27715	B242.00	Malignant neoplasm of anterior mediastinum
92720	B243.00	Malignant neoplasm of posterior mediastinum
61064	B24X.00	Malignant neoplasm of mediastinum, part unspecified
100232	B24y.00	Malig neop of other site of heart, thymus and mediastinum
66750	B24z.00	Malignant neoplasm of heart, thymus and mediastinum NOS
39531	B25..00	Malig neo, overlapping lesion of heart, mediastinum & pleura
66646	B26..00	Malignant neoplasm, overlap lesion of resp & intrathor orgs
44356	B2z..00	Malig neop other/ill-defined sites resp/intrathoracic organs
65793	B2z0.00	Malig neop of upper respiratory tract, part unspecified
29283	B2zy.00	Malignant neoplasm of other site of respiratory tract
42569	B2zz.00	Malignant neoplasm of respiratory tract NOS
18608	B3...00	Malig neop of bone, connective tissue, skin and breast
9902	B3...11	Carcinoma of bone, connective tissue, skin and breast
12539	B3...12	Sarcoma of bone and connective tissue
18314	B30..00	Malignant neoplasm of bone and articular cartilage
59036	B300.00	Malignant neoplasm of bones of skull and face
53594	B300000	Malignant neoplasm of ethmoid bone
53599	B300100	Malignant neoplasm of frontal bone
59520	B300200	Malignant neoplasm of malar bone

95458	B300300	Malignant neoplasm of nasal bone
55953	B300400	Malignant neoplasm of occipital bone
50298	B300500	Malignant neoplasm of orbital bone
54747	B300600	Malignant neoplasm of parietal bone
55595	B300700	Malignant neoplasm of sphenoid bone
62104	B300800	Malignant neoplasm of temporal bone
50299	B300900	Malignant neoplasm of zygomatic bone
17475	B300A00	Malignant neoplasm of maxilla
96445	B300B00	Malignant neoplasm of turbinate
44452	B300C00	Malignant neoplasm of vomer
69146	B300z00	Malignant neoplasm of bones of skull and face NOS
33833	B301.00	Malignant neoplasm of mandible
16704	B302.00	Malignant neoplasm of vertebral column
46939	B302000	Malignant neoplasm of cervical vertebra
32372	B302100	Malignant neoplasm of thoracic vertebra
54691	B302200	Malignant neoplasm of lumbar vertebra
49701	B302z00	Malignant neoplasm of vertebral column NOS
27528	B303.00	Malignant neoplasm of ribs, sternum and clavicle
37842	B303000	Malignant neoplasm of rib
49491	B303100	Malignant neoplasm of sternum
66639	B303200	Malignant neoplasm of clavicle
60403	B303300	Malignant neoplasm of costal cartilage
67763	B303400	Malignant neoplasm of costo-vertebral joint
54493	B303500	Malignant neoplasm of xiphoid process
51237	B303z00	Malignant neoplasm of rib, sternum and clavicle NOS
71810	B304.00	Malignant neoplasm of scapula and long bones of upper arm
49054	B304000	Malignant neoplasm of scapula
105797	B304100	Malignant neoplasm of acromion
61741	B304200	Malignant neoplasm of humerus
92371	B304300	Malignant neoplasm of radius
64848	B304400	Malignant neoplasm of ulna
65880	B304z00	Malig neop of scapula and long bones of upper arm NOS
73530	B305.00	Malignant neoplasm of hand bones
106069	B305.11	Malignant neoplasm of carpal bones
72464	B305.12	Malignant neoplasm of metacarpal bones
57988	B305000	Malignant neoplasm of carpal bone - scaphoid
69104	B305100	Malignant neoplasm of carpal bone - lunate
108638	B305A00	Malignant neoplasm of third metacarpal bone
94427	B305C00	Malignant neoplasm of fifth metacarpal bone
86812	B305D00	Malignant neoplasm of phalanges of hand
73556	B305z00	Malignant neoplasm of hand bones NOS
54631	B306.00	Malignant neoplasm of pelvic bones, sacrum and coccyx
44609	B306000	Malignant neoplasm of ilium
59223	B306100	Malignant neoplasm of ischium
51921	B306200	Malignant neoplasm of pubis
40966	B306300	Malignant neoplasm of sacral vertebra

66908	B306400	Malignant neoplasm of coccygeal vertebra
50152	B306500	Malignant sacral teratoma
38938	B306z00	Malignant neoplasm of pelvis, sacrum or coccyx NOS
68055	B307.00	Malignant neoplasm of long bones of leg
56513	B307000	Malignant neoplasm of femur
50402	B307100	Malignant neoplasm of fibula
40814	B307200	Malignant neoplasm of tibia
62630	B307z00	Malignant neoplasm of long bones of leg NOS
105475	B308.00	Malignant neoplasm of short bones of leg
95182	B308100	Malignant neoplasm of talus
72212	B308200	Malignant neoplasm of calcaneum
34878	B308300	Malignant neoplasm of medial cuneiform
69927	B308800	Malignant neoplasm of first metatarsal bone
92382	B308B00	Malignant neoplasm of fourth metatarsal bone
58949	B308D00	Malignant neoplasm of phalanges of foot
103354	B308z00	Malignant neoplasm of short bones of leg NOS
67451	B30W.00	Malignant neoplasm/overlap lesion/bone+articulr cartilage
43614	B30X.00	Malignant neoplasm/bones+articular cartilage/limb,unspfd
16075	B30z.00	Malignant neoplasm of bone and articular cartilage NOS
19437	B30z000	Osteosarcoma
34451	B31..00	Malignant neoplasm of connective and other soft tissue
43475	B310.00	Malig neop of connective and soft tissue head, face and neck
59382	B310000	Malignant neoplasm of soft tissue of head
40014	B310100	Malignant neoplasm of soft tissue of face
48517	B310200	Malignant neoplasm of soft tissue of neck
60035	B310300	Malignant neoplasm of cartilage of ear
49463	B310400	Malignant neoplasm of tarsus of eyelid
108389	B310500	Malignant neoplasm soft tissues of cervical spine
73718	B310z00	Malig neop connective and soft tissue head, face, neck NOS
53989	B311.00	Malig neop connective and soft tissue upper limb/shoulder
50222	B311000	Malignant neoplasm of connective and soft tissue of shoulder
64345	B311100	Malignant neoplasm of connective and soft tissue, upper arm
57482	B311200	Malignant neoplasm of connective and soft tissue of fore-arm
19321	B311300	Malignant neoplasm of connective and soft tissue of hand
91586	B311400	Malignant neoplasm of connective and soft tissue of finger
63988	B311500	Malignant neoplasm of connective and soft tissue of thumb
104913	B311z00	Malig neop connective soft tissue upper limb/shoulder NOS
66088	B312.00	Malig neop of connective and soft tissue of hip and leg
102949	B312000	Malignant neoplasm of connective and soft tissue of hip
44805	B312100	Malig neop of connective and soft tissue thigh and upper leg
54965	B312200	Malig neop connective and soft tissue of popliteal space
30542	B312300	Malig neop of connective and soft tissue of lower leg
54222	B312400	Malignant neoplasm of connective and soft tissue of foot
99572	B312500	Malignant neoplasm of connective and soft tissue of toe
90546	B312z00	Malig neop connective and soft tissue hip and leg NOS
22290	B313.00	Malignant neoplasm of connective and soft tissue of thorax

29160	B313000	Malignant neoplasm of connective and soft tissue of axilla
54186	B313100	Malignant neoplasm of diaphragm
72522	B313200	Malignant neoplasm of great vessels
104139	B313300	Malig neoplasm of connective and soft tissues of thor spine
98408	B313z00	Malig neop of connective and soft tissue of thorax NOS
45071	B314.00	Malignant neoplasm of connective and soft tissue of abdomen
66488	B314000	Malig neop of connective and soft tissue of abdominal wall
94272	B314100	Malig neoplasm of connective and soft tissues of lumb spine
60247	B314z00	Malig neop of connective and soft tissue of abdomen NOS
51965	B315.00	Malignant neoplasm of connective and soft tissue of pelvis
70463	B315000	Malignant neoplasm of connective and soft tissue of buttock
67324	B315100	Malig neop of connective and soft tissue of inguinal region
59152	B315200	Malignant neoplasm of connective and soft tissue of perineum
58836	B315z00	Malig neop of connective and soft tissue of pelvis NOS
57471	B316.00	Malig neop of connective and soft tissue trunk unspecified
65233	B31y.00	Malig neop connective and soft tissue other specified site
15182	B31z.00	Malignant neoplasm of connective and soft tissue, site NOS
104128	B31z000	Kaposi's sarcoma of soft tissue
865	B32..00	Malignant melanoma of skin
70637	B320.00	Malignant melanoma of lip
54632	B321.00	Malignant melanoma of eyelid including canthus
57260	B322.00	Malignant melanoma of ear and external auricular canal
59061	B322000	Malignant melanoma of auricle (ear)
102145	B322100	Malignant melanoma of external auditory meatus
73744	B322z00	Malignant melanoma of ear and external auricular canal NOS
47252	B323.00	Malignant melanoma of other and unspecified parts of face
41278	B323000	Malignant melanoma of external surface of cheek
71136	B323100	Malignant melanoma of chin
47094	B323200	Malignant melanoma of eyebrow
68133	B323300	Malignant melanoma of forehead
45139	B323400	Malignant melanoma of external surface of nose
58958	B323500	Malignant melanoma of temple
67806	B323z00	Malignant melanoma of face NOS
65625	B324.00	Malignant melanoma of scalp and neck
55881	B324000	Malignant melanoma of scalp
45306	B324100	Malignant melanoma of neck
99257	B324z00	Malignant melanoma of scalp and neck NOS
38689	B325.00	Malignant melanoma of trunk (excluding scrotum)
49814	B325000	Malignant melanoma of axilla
32768	B325100	Malignant melanoma of breast
53629	B325200	Malignant melanoma of buttock
34259	B325300	Malignant melanoma of groin
109002	B325400	Malignant melanoma of perianal skin
95629	B325500	Malignant melanoma of perineum
43715	B325600	Malignant melanoma of umbilicus
43463	B325700	Malignant melanoma of back

51209	B325800	Malignant melanoma of chest wall
45760	B325z00	Malignant melanoma of trunk, excluding scrotum, NOS
65164	B326.00	Malignant melanoma of upper limb and shoulder
50505	B326000	Malignant melanoma of shoulder
54685	B326100	Malignant melanoma of upper arm
45755	B326200	Malignant melanoma of fore-arm
62475	B326300	Malignant melanoma of hand
25602	B326400	Malignant melanoma of finger
63997	B326500	Malignant melanoma of thumb
55292	B326z00	Malignant melanoma of upper limb or shoulder NOS
46255	B327.00	Malignant melanoma of lower limb and hip
73536	B327000	Malignant melanoma of hip
51873	B327100	Malignant melanoma of thigh
54305	B327200	Malignant melanoma of knee
39878	B327300	Malignant melanoma of popliteal fossa area
37872	B327400	Malignant melanoma of lower leg
42714	B327500	Malignant melanoma of ankle
61246	B327600	Malignant melanoma of heel
41490	B327700	Malignant melanoma of foot
36899	B327800	Malignant melanoma of toe
53369	B327900	Malignant melanoma of great toe
64327	B327z00	Malignant melanoma of lower limb or hip NOS
42153	B32y.00	Malignant melanoma of other specified skin site
96585	B32y000	Overlapping malignant melanoma of skin
28556	B32z.00	Malignant melanoma of skin NOS
24375	B339.00	Dermatofibrosarcoma protuberans
3968	B34..00	Malignant neoplasm of female breast
348	B34..11	Ca female breast
26853	B340.00	Malignant neoplasm of nipple and areola of female breast
23380	B340000	Malignant neoplasm of nipple of female breast
64686	B340100	Malignant neoplasm of areola of female breast
59831	B340z00	Malignant neoplasm of nipple or areola of female breast NOS
31546	B341.00	Malignant neoplasm of central part of female breast
29826	B342.00	Malignant neoplasm of upper-inner quadrant of female breast
45222	B343.00	Malignant neoplasm of lower-inner quadrant of female breast
23399	B344.00	Malignant neoplasm of upper-outer quadrant of female breast
42070	B345.00	Malignant neoplasm of lower-outer quadrant of female breast
20685	B346.00	Malignant neoplasm of axillary tail of female breast
49148	B347.00	Malignant neoplasm, overlapping lesion of breast
56715	B34y.00	Malignant neoplasm of other site of female breast
95057	B34y000	Malignant neoplasm of ectopic site of female breast
38475	B34yz00	Malignant neoplasm of other site of female breast NOS
9470	B34z.00	Malignant neoplasm of female breast NOS
19423	B35..00	Malignant neoplasm of male breast
54494	B350.00	Malignant neoplasm of nipple and areola of male breast
68480	B350000	Malignant neoplasm of nipple of male breast

67884	B350100	Malignant neoplasm of areola of male breast
54202	B35z.00	Malignant neoplasm of other site of male breast
95323	B35z000	Malignant neoplasm of ectopic site of male breast
48809	B35zz00	Malignant neoplasm of male breast NOS
105488	B36..00	Local recurrence of malignant tumour of breast
19389	B3y..00	Malig neop of bone, connective tissue, skin and breast OS
41011	B3z..00	Malig neop of bone, connective tissue, skin and breast NOS
13252	B4...00	Malignant neoplasm of genitourinary organ
16874	B4...11	Carcinoma of genitourinary organ
2744	B40..00	Malignant neoplasm of uterus, part unspecified
2747	B41..00	Malignant neoplasm of cervix uteri
3230	B41..11	Cervical carcinoma (uterus)
48820	B410.00	Malignant neoplasm of endocervix
57235	B410000	Malignant neoplasm of endocervical canal
53103	B410100	Malignant neoplasm of endocervical gland
50285	B410z00	Malignant neoplasm of endocervix NOS
50297	B411.00	Malignant neoplasm of exocervix
58094	B412.00	Malignant neoplasm, overlapping lesion of cervix uteri
32955	B41y.00	Malignant neoplasm of other site of cervix
95505	B41y000	Malignant neoplasm of cervical stump
57719	B41y100	Malignant neoplasm of squamocolumnar junction of cervix
43435	B41yz00	Malignant neoplasm of other site of cervix NOS
28311	B41z.00	Malignant neoplasm of cervix uteri NOS
93762	B42..00	Malignant neoplasm of placenta
28003	B420.00	Choriocarcinoma
7046	B43..00	Malignant neoplasm of body of uterus
3213	B430.00	Malignant neoplasm of corpus uteri, excluding isthmus
72723	B430000	Malignant neoplasm of cornu of corpus uteri
68155	B430100	Malignant neoplasm of fundus of corpus uteri
2890	B430200	Malignant neoplasm of endometrium of corpus uteri
49400	B430211	Malignant neoplasm of endometrium
45793	B430300	Malignant neoplasm of myometrium of corpus uteri
45490	B430z00	Malignant neoplasm of corpus uteri NOS
43940	B431.00	Malignant neoplasm of isthmus of uterine body
59097	B431000	Malignant neoplasm of lower uterine segment
70729	B431z00	Malignant neoplasm of isthmus of uterine body NOS
16967	B432.00	Malignant neoplasm of overlapping lesion of corpus uteri
31608	B43y.00	Malignant neoplasm of other site of uterine body
33617	B43z.00	Malignant neoplasm of body of uterus NOS
19141	B44..00	Malignant neoplasm of ovary and other uterine adnexa
7805	B440.00	Malignant neoplasm of ovary
1986	B440.11	Cancer of ovary
49828	B441.00	Malignant neoplasm of fallopian tube
101778	B442.00	Malignant neoplasm of broad ligament
46153	B443.00	Malignant neoplasm of parametrium
97996	B44y.00	Malignant neoplasm of other site of uterine adnexa

65106	B44z.00	Malignant neoplasm of uterine adnexa NOS
4555	B45..00	Malig neop of other and unspecified female genital organs
37328	B450.00	Malignant neoplasm of vagina
10698	B450100	Malignant neoplasm of vaginal vault
60772	B450z00	Malignant neoplasm of vagina NOS
43761	B451.00	Malignant neoplasm of labia majora
47899	B451000	Malignant neoplasm of greater vestibular (Bartholin's) gland
59362	B451z00	Malignant neoplasm of labia majora NOS
58061	B452.00	Malignant neoplasm of labia minora
53910	B453.00	Malignant neoplasm of clitoris
4554	B454.00	Malignant neoplasm of vulva unspecified
11991	B454.11	Primary vulval cancer
26454	B45X.00	Malignant neoplasm/overlapping lesion/feml genital organs
95421	B45y.00	Malignant neoplasm of other specified female genital organ
27617	B45y000	Malignant neoplasm of overlapping lesion of vulva
20166	B45z.00	Malignant neoplasm of female genital organ NOS
780	B46..00	Malignant neoplasm of prostate
15148	B47..00	Malignant neoplasm of testis
64602	B470.00	Malignant neoplasm of undescended testis
7740	B470200	Seminoma of undescended testis
36325	B470300	Teratoma of undescended testis
96429	B470z00	Malignant neoplasm of undescended testis NOS
19475	B471.00	Malignant neoplasm of descended testis
21786	B471000	Seminoma of descended testis
9476	B471100	Teratoma of descended testis
91509	B471z00	Malignant neoplasm of descended testis NOS
38510	B47z.00	Malignant neoplasm of testis NOS
2961	B47z.11	Seminoma of testis
15989	B47z.12	Teratoma of testis
3541	B48..00	Malignant neoplasm of penis and other male genital organs
50681	B480.00	Malignant neoplasm of prepuce (foreskin)
17841	B481.00	Malignant neoplasm of glans penis
48743	B482.00	Malignant neoplasm of body of penis
43392	B483.00	Malignant neoplasm of penis, part unspecified
72127	B484.00	Malignant neoplasm of epididymis
63331	B485.00	Malignant neoplasm of spermatic cord
47767	B486.00	Malignant neoplasm of scrotum
52570	B487.00	Malignant neoplasm, overlapping lesion of penis
67949	B48y.00	Malignant neoplasm of other male genital organ
68161	B48y000	Malignant neoplasm of seminal vesicle
47668	B48y100	Malignant neoplasm of tunica vaginalis
68824	B48y200	Malignant neoplasm, overlapping lesion male genital orgs
92329	B48yz00	Malignant neoplasm of other male genital organ NOS
63224	B48z.00	Malignant neoplasm of penis and other male genital organ NOS
779	B49..00	Malignant neoplasm of urinary bladder
38862	B490.00	Malignant neoplasm of trigone of urinary bladder

44996	B491.00	Malignant neoplasm of dome of urinary bladder
35963	B492.00	Malignant neoplasm of lateral wall of urinary bladder
19162	B493.00	Malignant neoplasm of anterior wall of urinary bladder
42012	B494.00	Malignant neoplasm of posterior wall of urinary bladder
41571	B495.00	Malignant neoplasm of bladder neck
28241	B496.00	Malignant neoplasm of ureteric orifice
42023	B497.00	Malignant neoplasm of urachus
105388	B498.00	Local recurrence of malignant tumour of urinary bladder
36949	B49y.00	Malignant neoplasm of other site of urinary bladder
47801	B49y000	Malignant neoplasm, overlapping lesion of bladder
31102	B49z.00	Malignant neoplasm of urinary bladder NOS
13559	B4A..00	Malig neop of kidney and other unspecified urinary organs
18712	B4A..11	Renal malignant neoplasm
1599	B4A0.00	Malignant neoplasm of kidney parenchyma
7978	B4A0000	Hypernephroma
12389	B4A1.00	Malignant neoplasm of renal pelvis
27540	B4A1000	Malignant neoplasm of renal calyces
101608	B4A1100	Malignant neoplasm of ureteropelvic junction
54184	B4A1z00	Malignant neoplasm of renal pelvis NOS
15223	B4A2.00	Malignant neoplasm of ureter
15644	B4A3.00	Malignant neoplasm of urethra
72174	B4A4.00	Malignant neoplasm of paraurethral glands
44884	B4Ay.00	Malignant neoplasm of other urinary organs
59286	B4Ay000	Malignant neoplasm of overlapping lesion of urinary organs
29462	B4Az.00	Malignant neoplasm of kidney or urinary organs NOS
38931	B4y..00	Malignant neoplasm of genitourinary organ OS
52594	B4z..00	Malignant neoplasm of genitourinary organ NOS
10995	B5...00	Malignant neoplasm of other and unspecified sites
8693	B5...11	Carcinoma of other and unspecified sites
20160	B50..00	Malignant neoplasm of eye
98813	B500.00	Malig neop eyeball excl conjunctiva, cornea, retina, choroid
59041	B500000	Malignant neoplasm of ciliary body
59381	B500100	Malignant neoplasm of iris
106569	B500200	Malignant neoplasm of crystalline lens
56718	B500z00	Malignant neoplasm of eyeball NOS
45667	B501.00	Malignant neoplasm of orbit
86996	B501000	Malignant neoplasm of connective tissue of orbit
63104	B501z00	Malignant neoplasm of orbit NOS
64817	B502.00	Malignant neoplasm of lacrimal gland
63657	B503.00	Malignant neoplasm of conjunctiva
73992	B504.00	Malignant neoplasm of cornea
28069	B505.00	Malignant neoplasm of retina
15991	B506.00	Malignant neoplasm of choroid
71584	B507.00	Malignant neoplasm of lacrimal duct
101805	B507000	Malignant neoplasm of lacrimal sac
65357	B507100	Malignant neoplasm of nasolacrimal duct

45922	B508.00	Malignant neoplasm, overlapping lesion of eye and adnexa
108363	B509.00	Malignant melanoma of eye
40437	B50y.00	Malignant neoplasm of other specified site of eye
54956	B50z.00	Malignant neoplasm of eye NOS
18617	B51..00	Malignant neoplasm of brain
10851	B51..11	Cerebral tumour - malignant
15711	B510.00	Malignant neoplasm cerebrum (excluding lobes and ventricles)
48073	B510000	Malignant neoplasm of basal ganglia
61399	B510100	Malignant neoplasm of cerebral cortex
99913	B510300	Malignant neoplasm of globus pallidus
70942	B510400	Malignant neoplasm of hypothalamus
62126	B510500	Malignant neoplasm of thalamus
54133	B510z00	Malignant neoplasm of cerebrum NOS
42426	B511.00	Malignant neoplasm of frontal lobe
46792	B512.00	Malignant neoplasm of temporal lobe
67236	B512000	Malignant neoplasm of hippocampus
47556	B512z00	Malignant neoplasm of temporal lobe NOS
19226	B513.00	Malignant neoplasm of parietal lobe
39088	B514.00	Malignant neoplasm of occipital lobe
52511	B515.00	Malignant neoplasm of cerebral ventricles
46789	B515000	Malignant neoplasm of choroid plexus
45154	B516.00	Malignant neoplasm of cerebellum
44089	B517.00	Malignant neoplasm of brain stem
64557	B517000	Malignant neoplasm of cerebral peduncle
49132	B517100	Malignant neoplasm of medulla oblongata
93537	B517200	Malignant neoplasm of midbrain
91240	B517300	Malignant neoplasm of pons
68641	B517z00	Malignant neoplasm of brain stem NOS
71139	B51y.00	Malignant neoplasm of other parts of brain
59170	B51y000	Malignant neoplasm of corpus callosum
65241	B51y200	Malignant neoplasm, overlapping lesion of brain
100733	B51yz00	Malignant neoplasm of other part of brain NOS
41520	B51z.00	Malignant neoplasm of brain NOS
65458	B52..00	Malig neop of other and unspecified parts of nervous system
99621	B520.00	Malignant neoplasm of cranial nerves
64971	B520000	Malignant neoplasm of olfactory bulb
70126	B520100	Malignant neoplasm of optic nerve
65599	B520200	Malignant neoplasm of acoustic nerve
101086	B520z00	Malignant neoplasm of cranial nerves NOS
28919	B521.00	Malignant neoplasm of cerebral meninges
70104	B521z00	Malignant neoplasm of cerebral meninges NOS
51115	B522.00	Malignant neoplasm of spinal cord
49714	B523.00	Malignant neoplasm of spinal meninges
67211	B523z00	Malignant neoplasm of spinal meninges NOS
24235	B524.00	Malig neopl peripheral nerves and autonomic nervous system
63568	B524000	Malignant neoplasm of peripheral nerves of head, face & neck

61716	B524100	Malignant neoplasm of peripheral nerve,upp limb,incl should
89258	B524200	Malignant neoplasm of peripheral nerve of low limb, incl hip
63695	B524300	Malignant neoplasm of peripheral nerve of thorax
86046	B524400	Malignant neoplasm of peripheral nerve of abdomen
73988	B524500	Malignant neoplasm of peripheral nerve of pelvis
50777	B524600	Malignant neoplasm,overlap lesion periph nerve & auton ns
106654	B524W00	Mal neoplasm/periph nerves+autonomic nervous system,unspc
9622	B525.00	Malignant neoplasm of cauda equina
53504	B52W.00	Malig neopl, overlap lesion brain & other part of CNS
49875	B52X.00	Malignant neoplasm of meninges, unspecified
88144	B52y.00	Malignant neoplasm of other specified part of nervous system
56490	B52z.00	Malignant neoplasm of nervous system NOS
5637	B53..00	Malignant neoplasm of thyroid gland
30511	B54..00	Malig neop of other endocrine glands and related structures
28148	B540.00	Malignant neoplasm of adrenal gland
18231	B540.11	Phaeochromocytoma
61390	B540000	Malignant neoplasm of adrenal cortex
94220	B540100	Malignant neoplasm of adrenal medulla
70824	B540z00	Malignant neoplasm of adrenal gland NOS
4218	B541.00	Malignant neoplasm of parathyroid gland
59823	B542.00	Malignant neoplasm pituitary gland and craniopharyngeal duct
8550	B542000	Malignant neoplasm of pituitary gland
39899	B542100	Malignant neoplasm of craniopharyngeal duct
59718	B542z00	Malig neop pituitary gland or craniopharyngeal duct NOS
42460	B543.00	Malignant neoplasm of pineal gland
57047	B544.00	Malignant neoplasm of carotid body
50035	B545.00	Malignant neoplasm of aortic body and other paraganglia
51795	B545000	Malignant neoplasm of glomus jugulare
47840	B545100	Malignant neoplasm of aortic body
46905	B545200	Malignant neoplasm of coccygeal body
103995	B545z00	Malignant neoplasm of aortic body or paraganglia NOS
100083	B546.00	Neuroblastoma
87113	B54X.00	Malignant neoplasm-pluriglandular involvement,unspecified
90659	B54y.00	Malignant neoplasm of other specified endocrine gland
64195	B54z.00	Malig neop of endocrine gland or related structure NOS
9030	B55..00	Malignant neoplasm of other and ill-defined sites
68236	B550.00	Malignant neoplasm of head, neck and face
55098	B550000	Malignant neoplasm of head NOS
41931	B550100	Malignant neoplasm of cheek NOS
12490	B550200	Malignant neoplasm of nose NOS
51818	B550300	Malignant neoplasm of jaw NOS
16280	B550400	Malignant neoplasm of neck NOS
73510	B550500	Malignant neoplasm of supraclavicular fossa NOS
58903	B550z00	Malignant neoplasm of head, neck and face NOS
47286	B551.00	Malignant neoplasm of thorax
37618	B551000	Malignant neoplasm of axilla NOS

23861	B551100	Malignant neoplasm of chest wall NOS
97547	B551200	Malignant neoplasm of intrathoracic site NOS
64810	B551z00	Malignant neoplasm of thorax NOS
15976	B552.00	Malignant neoplasm of abdomen
52316	B553.00	Malignant neoplasm of pelvis
57854	B553000	Malignant neoplasm of inguinal region NOS
89916	B553100	Malignant neoplasm of presacral region
107126	B553200	Malignant neoplasm of sacrococcygeal region
55101	B553z00	Malignant neoplasm of pelvis NOS
27449	B554.00	Malignant neoplasm of upper limb NOS
31399	B555.00	Malignant neoplasm of lower limb NOS
42218	B55y.00	Malignant neoplasm of other specified sites
68787	B55y000	Malignant neoplasm of back NOS
67217	B55y100	Malignant neoplasm of trunk NOS
94355	B55y200	Malignant neoplasm of flank NOS
60052	B55yz00	Malignant neoplasm of specified site NOS
45267	B55z.00	Malignant neoplasm of other and ill defined site NOS
47810	B59..00	Malignant neoplasm of unspecified site
13569	B590.00	Disseminated malignancy NOS
6170	B590.11	Carcinomatosis
26034	B591.00	Other malignant neoplasm NOS
51352	B592.00	Malignant neoplasms of independent (primary) multiple sites
65466	B592X00	Kaposi's sarcoma of multiple organs
11035	B593.00	Primary malignant neoplasm of unknown site
104324	B595.00	Malignant tumour of unknown origin
54267	B59z.00	Malignant neoplasm of unspecified site NOS
49525	B59zX00	Kaposi's sarcoma, unspecified
38736	B5y..00	Malignant neoplasm of other and unspecified site OS
1056	B5z..00	Malignant neoplasm of other and unspecified site NOS
12323	B6...00	Malignant neoplasm of lymphatic and haemopoietic tissue
37112	B6...11	Malignant neoplasm of histiocytic tissue
41369	B60..00	Lymphosarcoma and reticulosarcoma
1481	B600.00	Reticulosarcoma
60242	B600000	Reticulosarcoma of unspecified site
71031	B600100	Reticulosarcoma of lymph nodes of head, face and neck
70374	B600300	Reticulosarcoma of intra-abdominal lymph nodes
95058	B600700	Reticulosarcoma of spleen
99240	B600z00	Reticulosarcoma NOS
27416	B601.00	Lymphosarcoma
71625	B601000	Lymphosarcoma of unspecified site
71238	B601100	Lymphosarcoma of lymph nodes of head, face and neck
62380	B601200	Lymphosarcoma of intrathoracic lymph nodes
64670	B601300	Lymphosarcoma of intra-abdominal lymph nodes
100352	B601500	Lymphosarcoma of lymph nodes of inguinal region and leg
103245	B601700	Lymphosarcoma of spleen
104790	B601800	Lymphosarcoma of lymph nodes of multiple sites

63723	B601z00	Lymphosarcoma NOS
21402	B602.00	Burkitt's lymphoma
59115	B602100	Burkitt's lymphoma of lymph nodes of head, face and neck
100006	B602200	Burkitt's lymphoma of intrathoracic lymph nodes
97577	B602300	Burkitt's lymphoma of intra-abdominal lymph nodes
92380	B602500	Burkitt's lymphoma of lymph nodes of inguinal region and leg
71304	B602z00	Burkitt's lymphoma NOS
99887	B60y.00	Other specified reticulosarcoma or lymphosarcoma
99951	B60z.00	Reticulosarcoma or lymphosarcoma NOS
2462	B61..00	Hodgkin's disease
104291	B61..11	Hodgkin lymphoma
65489	B610.00	Hodgkin's paragranuloma
100423	B610100	Hodgkin's paragranuloma of lymph nodes of head, face, neck
98840	B610300	Hodgkin's paragranuloma of intra-abdominal lymph nodes
44196	B611.00	Hodgkin's granuloma
98909	B611100	Hodgkin's granuloma of lymph nodes of head, face and neck
64036	B612.00	Hodgkin's sarcoma
68039	B612400	Hodgkin's sarcoma of lymph nodes of axilla and upper limb
38939	B613.00	Hodgkin's disease, lymphocytic-histiocytic predominance
71142	B613000	Hodgkin's, lymphocytic-histiocytic predominance unspec site
68330	B613100	Hodgkin's, lymphocytic-histiocytic pred of head, face, neck
92245	B613200	Hodgkin's, lymphocytic-histiocytic pred intrathoracic nodes
73532	B613300	Hodgkin's, lymphocytic-histiocytic pred intra-abdominal node
93951	B613500	Hodgkin's, lymphocytic-histiocytic pred inguinal and leg
95338	B613600	Hodgkin's, lymphocytic-histiocytic pred intrapelvic nodes
106911	B613700	Hodgkin's, lymphocytic-histiocytic predominance of spleen
104743	B613800	Hodgkin's, lymphocytic-histiocytic pred of multiple sites
29876	B613z00	Hodgkin's, lymphocytic-histiocytic predominance NOS
29178	B614.00	Hodgkin's disease, nodular sclerosis
57225	B614000	Hodgkin's disease, nodular sclerosis of unspecified site
55303	B614100	Hodgkin's nodular sclerosis of head, face and neck
67506	B614200	Hodgkin's nodular sclerosis of intrathoracic lymph nodes
61149	B614300	Hodgkin's nodular sclerosis of intra-abdominal lymph nodes
65483	B614400	Hodgkin's nodular sclerosis of lymph nodes of axilla and arm
105472	B614700	Hodgkin's disease, nodular sclerosis of spleen
19140	B614800	Hodgkin's nodular sclerosis of lymph nodes of multiple sites
63054	B614z00	Hodgkin's disease, nodular sclerosis NOS
49605	B615.00	Hodgkin's disease, mixed cellularity
97863	B615000	Hodgkin's disease, mixed cellularity of unspecified site
94407	B615100	Hodgkin's mixed cellularity of lymph nodes head, face, neck
58684	B615200	Hodgkin's mixed cellularity of intrathoracic lymph nodes
108886	B615500	Hodgkin's mixed cellularity of lymph nodes inguinal and leg
94005	B615z00	Hodgkin's disease, mixed cellularity NOS
67703	B616.00	Hodgkin's disease, lymphocytic depletion
95049	B616000	Hodgkin's lymphocytic depletion of unspecified site
63625	B616400	Hodgkin's lymphocytic depletion lymph nodes axilla and arm

101715	B616700	Hodgkin's disease, lymphocytic depletion of spleen
107032	B616800	Hodgkin's lymphocytic depletion lymph nodes multiple sites
101530	B616z00	Hodgkin's disease, lymphocytic depletion NOS
104895	B617.00	Nodular lymphocyte predominant Hodgkin lymphoma
105841	B618.00	Nodular sclerosis classical Hodgkin lymphoma
108775	B619.00	Mixed cellularity classical Hodgkin lymphoma
106597	B61B.00	Lymphocyte-rich classical Hodgkin lymphoma
104484	B61C.00	Other classical Hodgkin lymphoma
53397	B61z.00	Hodgkin's disease NOS
106349	B61z.11	Hodgkin lymphoma NOS
61662	B61z000	Hodgkin's disease NOS, unspecified site
59778	B61z100	Hodgkin's disease NOS of lymph nodes of head, face and neck
59755	B61z200	Hodgkin's disease NOS of intrathoracic lymph nodes
107804	B61z300	Hodgkin's disease NOS of intra-abdominal lymph nodes
91900	B61z400	Hodgkin's disease NOS of lymph nodes of axilla and arm
99012	B61z500	Hodgkin's disease NOS of lymph nodes inguinal region and leg
94279	B61z700	Hodgkin's disease NOS of spleen
97746	B61z800	Hodgkin's disease NOS of lymph nodes of multiple sites
42461	B61zz00	Hodgkin's disease NOS
33333	B62..00	Other malignant neoplasm of lymphoid and histiocytic tissue
5179	B620.00	Nodular lymphoma (Brill - Symmers disease)
66327	B620000	Nodular lymphoma of unspecified site
45264	B620100	Nodular lymphoma of lymph nodes of head, face and neck
105203	B620200	Nodular lymphoma of intrathoracic lymph nodes
92068	B620300	Nodular lymphoma of intra-abdominal lymph nodes
94995	B620500	Nodular lymphoma of lymph nodes of inguinal region and leg
58082	B620800	Nodular lymphoma of lymph nodes of multiple sites
65701	B620z00	Nodular lymphoma NOS
12006	B621.00	Mycosis fungoides
95949	B621000	Mycosis fungoides of unspecified site
91674	B621300	Mycosis fungoides of intra-abdominal lymph nodes
96379	B621400	Mycosis fungoides of lymph nodes of axilla and upper limb
72714	B621500	Mycosis fungoides of lymph nodes of inguinal region and leg
95012	B621800	Mycosis fungoides of lymph nodes of multiple sites
38005	B621z00	Mycosis fungoides NOS
35014	B622.00	Sezary's disease
100532	B622z00	Sezary's disease NOS
44267	B623.00	Malignant histiocytosis
69497	B623000	Malignant histiocytosis of unspecified site
94415	B623100	Malignant histiocytosis of lymph nodes head, face and neck
65642	B623300	Malignant histiocytosis of intra-abdominal lymph nodes
58871	B623z00	Malignant histiocytosis NOS
27330	B624.00	Leukaemic reticuloendotheliosis
5137	B624.11	Leukaemic reticuloendotheliosis
87335	B624.12	Hairy cell leukaemia
65122	B624000	Leukaemic reticuloendotheliosis of unspecified sites

65123	B624300	Leukaemic reticuloend of intra-abdominal lymph nodes
73777	B624z00	Leukaemic reticuloendotheliosis NOS
34926	B625.00	Letterer-Siwe disease
4870	B625.11	Histiocytosis X (acute, progressive)
102715	B625000	Letterer-Siwe disease of unspecified sites
102158	B625200	Letterer-Siwe disease of intrathoracic lymph nodes
54083	B625800	Letterer-Siwe disease of lymph nodes of multiple sites
47204	B625z00	Letterer-Siwe disease NOS
15036	B626.00	Malignant mast cell tumours
103900	B626000	Mast cell malignancy of unspecified site
100615	B626500	Mast cell malignancy of lymph nodes inguinal region and leg
31324	B626800	Mast cell malignancy of lymph nodes of multiple sites
89657	B626z00	Malignant mast cell tumour NOS
3604	B627.00	Non - Hodgkin's lymphoma
104391	B627.11	Non-Hodgkin lymphoma
28639	B627000	Follicular non-Hodgkin's small cleaved cell lymphoma
70842	B627100	Follicular non-Hodg mixed sml cleavd & lge cell lymphoma
49262	B627200	Follicular non-Hodgkin's large cell lymphoma
50668	B627300	Diffuse non-Hodgkin's small cell (diffuse) lymphoma
108182	B627400	Diffuse non-Hodgkin's small cleaved cell (diffuse) lymphoma
50695	B627500	Diffuse non-Hodgkin mixed sml & lge cell (diffuse) lymphoma
53551	B627600	Diffuse non-Hodgkin's immunoblastic (diffuse) lymphoma
17460	B627700	Diffuse non-Hodgkin's lymphoblastic (diffuse) lymphoma
65180	B627800	Diffuse non-Hodgkin's lymphoma undifferentiated (diffuse)
95715	B627900	Mucosa-associated lymphoma
95545	B627911	Maltoma
101114	B627A00	Diffuse non-Hodgkin's large cell lymphoma
31576	B627B00	Other types of follicular non-Hodgkin's lymphoma
21549	B627C00	Follicular non-Hodgkin's lymphoma
17182	B627C11	Follicular lymphoma NOS
70509	B627D00	Diffuse non-Hodgkin's centroblastic lymphoma
102594	B627E00	Diffuse large B-cell lymphoma
105966	B627F00	Extranod marg zone B-cell lymphom mucosa-assoc lymphoid tiss
105038	B627G00	Mediastinal (thymic) large B-cell lymphoma
31794	B627W00	Unspecified B-cell non-Hodgkin's lymphoma
39798	B627X00	Diffuse non-Hodgkin's lymphoma, unspecified
104152	B628.00	Follicular lymphoma
105889	B628000	Follicular lymphoma grade 1
105095	B628100	Follicular lymphoma grade 2
107166	B628200	Follicular lymphoma grade 3
105020	B628300	Follicular lymphoma grade 3a
107973	B628400	Follicular lymphoma grade 3b
106969	B628500	Diffuse follicle centre lymphoma
108719	B628600	Cutaneous follicle centre lymphoma
106063	B628700	Other types of follicular lymphoma
105792	B629.00	Multifocal multisystemic dissem Langerhans-cell histiocytosi

105335	B62A.00	Sarcoma of dendritic cells
105762	B62C.00	Unifocal Langerhans-cell histiocytosis
105083	B62D.00	Histiocytic sarcoma
105085	B62E.00	T/NK-cell lymphoma
105559	B62E100	Anaplastic large cell lymphoma, ALK-positive
105955	B62E200	Anaplastic large cell lymphoma, ALK-negative
104862	B62E300	Cutaneous T-cell lymphoma
107949	B62E500	Hepatosplenic T-cell lymphoma
105709	B62E600	Enteropathy-associated T-cell lymphoma
105925	B62E700	Subcutaneous panniculitic T-cell lymphoma
105375	B62E800	Blastic NK-cell lymphoma
105636	B62E900	Angioimmunoblastic T-cell lymphoma
105286	B62EA00	Primary cutaneous CD30-positive T-cell proliferations
104934	B62Ew00	Other mature T/NK-cell lymphoma
106884	B62F.00	Nonfollicular lymphoma
106867	B62F.11	Non-follicular lymphoma
104386	B62F000	Small cell B-cell lymphoma
104620	B62F100	Mantle cell lymphoma
104412	B62F200	Lymphoblastic (diffuse) lymphoma
17887	B62x.00	Malignant lymphoma otherwise specified
90201	B62x000	T-zone lymphoma
57737	B62x100	Lymphoepithelioid lymphoma
12464	B62x200	Peripheral T-cell lymphoma
62437	B62x400	Malignant reticulosis
58962	B62x500	Malignant immunoproliferative small intestinal disease
95630	B62x600	True histiocytic lymphoma
44318	B62xX00	Oth and unspecif peripheral & cutaneous T-cell lymphomas
12335	B62y.00	Malignant lymphoma NOS
57427	B62y000	Malignant lymphoma NOS of unspecified site
50696	B62y100	Malignant lymphoma NOS of lymph nodes of head, face and neck
72725	B62y200	Malignant lymphoma NOS of intrathoracic lymph nodes
42579	B62y300	Malignant lymphoma NOS of intra-abdominal lymph nodes
34089	B62y400	Malignant lymphoma NOS of lymph nodes of axilla and arm
63105	B62y500	Malignant lymphoma NOS of lymph node inguinal region and leg
71262	B62y600	Malignant lymphoma NOS of intrapelvic lymph nodes
60092	B62y700	Malignant lymphoma NOS of spleen
15504	B62y800	Malignant lymphoma NOS of lymph nodes of multiple sites
15027	B62yz00	Malignant lymphoma NOS
65434	B62z.00	Malignant neoplasms of lymphoid and histiocytic tissue NOS
108037	B62z000	Unspec malig neop lymphoid/histiocytic of unspecified site
64427	B62z100	Unspec malig neop lymphoid/histiocytic lymph node head/neck
93384	B62z200	Unspec malig neop lymphoid/histiocytic of intrathoracic node
103353	B62z300	Unspec malig neop lymphoid/histiocytic intra-abdominal nodes
107638	B62z400	Unspec malig neop lymphoid/histiocytic lymph node axilla/arm
71609	B62z500	Unspec malig neop lymphoid/histiocytic nodes inguinal/leg
101465	B62z800	Unspec malig neop lymphoid/histiocytic of multiple sites

95792	B62zz00	Lymphoid and histiocytic malignancy NOS
70716	B62zz11	Immunoproliferative neoplasm
37182	B63..00	Multiple myeloma and immunoproliferative neoplasms
4944	B630.00	Multiple myeloma
43552	B630.11	Kahler's disease
15211	B630.12	Myelomatosis
22158	B630000	Malignant plasma cell neoplasm, extramedullary plasmacytoma
19028	B630100	Solitary myeloma
21329	B630200	Plasmacytoma NOS
46042	B630300	Lambda light chain myeloma
104418	B630400	Solitary plasmacytoma
39187	B631.00	Plasma cell leukaemia
64567	B63y.00	Other immunoproliferative neoplasms
43450	B63z.00	Immunoproliferative neoplasm or myeloma NOS
19372	B64..00	Lymphoid leukaemia
4222	B64..11	Lymphatic leukaemia
4251	B640.00	Acute lymphoid leukaemia
104325	B640000	B-cell acute lymphoblastic leukaemia
8625	B641.00	Chronic lymphoid leukaemia
27790	B641.11	Chronic lymphatic leukaemia
104328	B641000	B-cell chronic lymphocytic leukaemia
107017	B641011	Chronic lymphocytic leukaemia of B-cell type
107052	B641100	Clinical stage A chronic lymphocytic leukaemia
106924	B641200	Clinical stage B chronic lymphocytic leukaemia
107163	B641300	Clinical stage C chronic lymphocytic leukaemia
72774	B642.00	Subacute lymphoid leukaemia
49725	B64y.00	Other lymphoid leukaemia
31586	B64y100	Prolymphocytic leukaemia
37461	B64y200	Adult T-cell leukaemia
108656	B64y300	B-cell prolymphocytic leukaemia
107643	B64y400	T-cell prolymphocytic leukaemia
104939	B64y500	Adult T-cell lymphoma/leukaemia (HTLV-1-associated)
38331	B64yz00	Other lymphoid leukaemia NOS
38914	B64z.00	Lymphoid leukaemia NOS
7176	B65..00	Myeloid leukaemia
4413	B650.00	Acute myeloid leukaemia
10726	B651.00	Chronic myeloid leukaemia
31701	B651.11	Chronic granulocytic leukaemia
100786	B651000	Chronic eosinophilic leukaemia
105957	B651100	Chronic myeloid leukaemia, BCR/ABL positive
102783	B651200	Chronic neutrophilic leukaemia
107236	B651300	Atypical chronic myeloid leukaemia, BCR/ABL negative
27520	B651z00	Chronic myeloid leukaemia NOS
63475	B652.00	Subacute myeloid leukaemia
70724	B653.00	Myeloid sarcoma
52327	B653000	Chloroma

39629	B653100	Granulocytic sarcoma
104788	B654.00	Acute myeloblastic leukaemia
27664	B65y100	Acute promyelocytic leukaemia
66089	B65yz00	Other myeloid leukaemia NOS
33344	B65z.00	Myeloid leukaemia NOS
35875	B66..00	Monocytic leukaemia
108715	B66..11	Histiocytic leukaemia
67700	B66..12	Monoblastic leukaemia
19974	B660.00	Acute monocytic leukaemia
27458	B661.00	Chronic monocytic leukaemia
101606	B662.00	Subacute monocytic leukaemia
108424	B663.00	Acute monoblastic leukaemia
99015	B66y.00	Other monocytic leukaemia
103645	B66yz00	Other monocytic leukaemia NOS
93342	B66z.00	Monocytic leukaemia NOS
37272	B67..00	Other specified leukaemia
42539	B670.00	Acute erythraemia and erythroleukaemia
27340	B670.11	Di Guglielmo's disease
37468	B671.00	Chronic erythraemia
63653	B671.11	Heilmeyer - Schoner disease
57671	B672.00	Megakaryocytic leukaemia
65777	B672.11	Thrombocytic leukaemia
65721	B673.00	Mast cell leukaemia
50858	B674.00	Acute panmyelosis
28276	B675.00	Acute myelofibrosis
104273	B677.00	Myelodysplastic and myeloproliferative disease
94174	B67y.00	Other and unspecified leukaemia
72197	B67y000	Lymphosarcoma cell leukaemia
99413	B67yz00	Other and unspecified leukaemia NOS
30632	B67z.00	Other specified leukaemia NOS
25191	B68..00	Leukaemia of unspecified cell type
4072	B680.00	Acute leukaemia NOS
16416	B681.00	Chronic leukaemia NOS
54793	B682.00	Subacute leukaemia NOS
34692	B68y.00	Other leukaemia of unspecified cell type
4250	B68z.00	Leukaemia NOS
20440	B69..00	Myelomonocytic leukaemia
61500	B690.00	Acute myelomonocytic leukaemia
22050	B691.00	Chronic myelomonocytic leukaemia
104475	B692.00	Subacute myelomonocytic leukaemia
105069	B693.00	Juvenile myelomonocytic leukaemia
30646	B6y..00	Malignant neoplasm lymphatic or haematopoietic tissue OS
6115	B6y0.00	Myeloproliferative disorder
17056	B6y0.11	Myeloproliferative disease
39336	B6y1.00	Myelosclerosis with myeloid metaplasia
49301	B6z..00	Malignant neoplasm lymphatic or haematopoietic tissue NOS

50290	B6z0.00	Kaposi's sarcoma of lymph nodes
7473	B8...00	Carcinoma in situ
60511	B80..00	Carcinoma in situ of digestive organs
33250	B80..11	Ca-in-situ of G.I. tract
95390	B800.00	Carcinoma in situ of lip, oral cavity and pharynx
37505	B800.11	Carcinoma in situ of oral cavity
42129	B800.12	Carcinoma in situ of pharynx
47737	B800000	Carcinoma in situ of lip
27944	B800100	Carcinoma in situ of tongue
50288	B800200	Carcinoma in situ of salivary glands
57866	B800300	Carcinoma in situ of gums
24801	B800400	Carcinoma in situ of floor of mouth
34823	B800500	Carcinoma in situ of cheek
30966	B800600	Carcinoma in situ of palate
36104	B800700	Carcinoma in situ of nasopharynx
50419	B800800	Carcinoma in situ of oropharynx
44663	B800900	Carcinoma in situ of hypopharynx
37187	B800z00	Carcinoma in situ of lip, oral cavity and pharynx NOS
8244	B801.00	Carcinoma in situ of oesophagus
99155	B801000	Carcinoma in situ of upper 1/3 oesophagus
64274	B801100	Carcinoma in situ of middle 1/3 oesophagus
56077	B801200	Carcinoma in situ of lower 1/3 oesophagus
44228	B801z00	Carcinoma in situ of oesophagus NOS
17093	B802.00	Carcinoma in situ of stomach
17258	B802000	Carcinoma in situ of cardia of stomach
72947	B802100	Carcinoma in situ of fundus of stomach
63087	B802200	Carcinoma in situ of body of stomach
51748	B802300	Carcinoma in situ of pyloric antrum
58883	B802400	Carcinoma in situ of pyloric canal
37774	B802z00	Carcinoma in situ of stomach NOS
6903	B803.00	Carcinoma in situ of colon
39080	B803000	Carcinoma in situ of hepatic flexure of colon
37125	B803100	Carcinoma in situ of transverse colon
47667	B803200	Carcinoma in situ of descending colon
17144	B803300	Carcinoma in situ of sigmoid colon
16916	B803400	Carcinoma in situ of caecum
47656	B803500	Carcinoma in situ of appendix
31893	B803600	Carcinoma in situ of ascending colon
22699	B803700	Carcinoma in situ of splenic flexure of colon
105228	B803800	High grade dysplasia of colon
33561	B803z00	Carcinoma in situ of colon NOS
60477	B804.00	Carcinoma in situ of rectum and rectosigmoid junction
27811	B804000	Carcinoma in situ of rectosigmoid junction
29975	B804100	Carcinoma in situ of rectum
38883	B804z00	Carcinoma in situ of rectum or rectosigmoid junction NOS
51054	B805.00	Carcinoma in situ of anal canal

34094	B805000	Anal intraepithelial neoplasia grade III
12273	B806.00	Carcinoma in situ of anus NOS
22392	B807.00	Carcinoma in situ of other and unspecified small intestine
45070	B807000	Carcinoma in situ of duodenum
63804	B807100	Carcinoma in situ of jejunum
45217	B807200	Carcinoma in situ of ileum
100183	B807300	Carcinoma in situ of Meckel's diverticulum
70728	B807z00	Carcinoma in situ other and unspecified small intestine NOS
66673	B808.00	Carcinoma in situ of liver and biliary system
51934	B808.11	Carcinoma in situ of biliary system
25310	B808000	Carcinoma in situ of liver
99580	B808100	Carcinoma in situ of intrahepatic bile ducts
37501	B808200	Carcinoma in situ of hepatic duct
46594	B808300	Carcinoma in situ of gall bladder
73164	B808400	Carcinoma in situ of cystic duct
64089	B808500	Carcinoma in situ of common bile duct
21792	B808600	Carcinoma in situ of ampulla of Vater
98540	B808z00	Carcinoma in situ of liver or biliary system NOS
44166	B80z.00	Carcinoma in situ of other and unspecified digestive organs
16931	B80z000	Carcinoma in situ of pancreas
64700	B80z100	Carcinoma in situ of spleen
64050	B81..00	Carcinoma in situ of respiratory system
11403	B810.00	Carcinoma in situ of larynx
35772	B810000	Carcinoma in situ of thyroid cartilage
36948	B810100	Carcinoma in situ of cricoid cartilage
53460	B810200	Carcinoma in situ of epiglottis
65953	B810300	Carcinoma in situ of arytenoid cartilage
31860	B810600	Carcinoma in situ of aryepiglottic fold
73076	B810700	Carcinoma in situ of vestibular fold
7697	B810800	Carcinoma in situ of vocal fold - glottis
10375	B810811	Carcinoma in situ of glottis
53882	B810z00	Carcinoma in situ of larynx NOS
51714	B811.00	Carcinoma in situ of trachea
9267	B812.00	Carcinoma in situ of bronchus and lung
49159	B812000	Carcinoma in situ of carina of bronchus
35058	B812100	Carcinoma in situ of main bronchus
37579	B812200	Carcinoma in situ of upper lobe bronchus and lung
47897	B812300	Carcinoma in situ of middle lobe bronchus and lung
52373	B812400	Carcinoma in situ of lower lobe bronchus and lung
25372	B812z00	Carcinoma in situ of bronchus or lung NOS
97954	B81y.00	Carcinoma in situ of other specified part respiratory system
59426	B81y.11	Carcinoma in situ of nasal sinuses
46497	B81y000	Carcinoma in situ of pleura
39717	B81y100	Carcinoma in situ of nasal cavity
97200	B81y400	Carcinoma in situ of Eustachian tube
68135	B81y500	Carcinoma in situ of mastoid air cells

43380	B81y600	Carcinoma in situ of maxillary sinus
26846	B81y700	Carcinoma in situ of ethmoidal sinus
39064	B81y900	Carcinoma in situ of sphenoidal sinus
95559	B81yz00	Carcinoma in situ of specified parts respiratory system NOS
62610	B81z.00	Carcinoma in situ of respiratory organ NOS
19686	B828.00	Melanoma in situ of skin
46536	B828000	Melanoma in situ of lip
37108	B828100	Melanoma in situ of eyelid, including canthus
72032	B828200	Melanoma in situ of ear and external auricular canal
97858	B828300	Melanoma in situ of scalp and neck
59768	B828400	Melanoma in situ of trunk
56694	B828500	Melanoma in situ of upper limb, including shoulder
47850	B828600	Melanoma in situ of lower limb, including hip
49572	B828700	Melanoma in situ of scalp
52332	B828800	Melanoma in situ of back of hand
71044	B828900	Melanoma in situ of back
54246	B828W00	Melanoma in situ, unspecified
61989	B828X00	Melanoma in situ of other and unspecified parts of face
45681	B83..00	Carcinoma in situ of breast and genitourinary system
7833	B830.00	Carcinoma in situ of breast
10387	B830000	Lobular carcinoma in situ of breast
18694	B830100	Intraductal carcinoma in situ of breast
3279	B831.00	Carcinoma in situ of cervix uteri
4087	B831.11	CIN III - carcinoma in situ of cervix
5295	B831.12	Cervical intraepithelial neoplasia
21886	B831.13	Cervical intraepithelial neoplasia grade III
24228	B831000	Carcinoma in situ of endocervix
50126	B831100	Carcinoma in situ of exocervix
29898	B832.00	Carcinoma in situ of other and unspecified parts of uterus
61803	B832.11	Carcinoma in situ of body of uterus
7904	B832000	Carcinoma in situ of endometrium
44915	B833.00	Carcinoma in situ other and unspecified female genital organ
17137	B833000	Carcinoma in situ of ovary
59499	B833100	Carcinoma in situ of fallopian tube
34946	B833200	Carcinoma in situ of vagina
12119	B833300	Carcinoma in situ of vulva
3281	B833311	Vulval intraepithelial neoplasia
97096	B833400	Vulval intraepithelial neoplasia grade 1
96999	B833500	Vulval intraepithelial neoplasia grade 2
97107	B833600	Vulval intraepithelial neoplasia grade 3
102476	B833700	Vaginal intraepithelial neoplasia grade 1
101708	B833800	Vaginal intraepithelial neoplasia grade 2
102599	B833900	Vaginal intraepithelial neoplasia grade 3
69208	B833z00	Carcinoma in situ of female genital organs NOS
6328	B834.00	Carcinoma in situ of prostate
54599	B834000	High grade prostatic intraepithelial neoplasia

105236	B834100	Prostatic intraepithelial neoplasia
27311	B835.00	Carcinoma in situ of penis
107958	B836.00	Carcinoma in situ other and unspecified male genital organs
8177	B836000	Carcinoma in situ of testis
58879	B836300	Carcinoma in situ of scrotum
7187	B837.00	Carcinoma in situ of bladder
68358	B83z.00	Carcinoma in situ of urinary organs NOS
38611	B8y..00	Carcinoma in situ of other and unspecified sites
58124	B8y0.00	Carcinoma in situ of eye
53349	B8yy.00	Carcinoma in situ of other specified site
8958	B8yy000	Carcinoma in situ of thyroid gland
46478	B8yy100	Carcinoma in situ of adrenal gland
58016	B8yy200	Carcinoma in situ of parathyroid gland
45909	B8yy300	Carcinoma in situ of pituitary gland
56640	B8yyz00	Carcinoma in situ of other specified site NOS
35136	B8z..00	Carcinoma in situ NOS
19657	B911000	Malignant hydatidiform mole
101813	B911012	Invasive mole - placenta
5136	B911013	Choriocarcinoma
2481	B934.00	Polycythaemia vera
5542	B934.11	Polycythaemia rubra vera
36790	B934.12	Primary polycythaemia
20609	B937.00	Neop uncertain behaviour other lymphatic/haematopoietic tiss
72551	B937.11	Neoplasm of uncertain behaviour of blood
31560	B937.12	Idiopathic thrombocythaemia
14927	B937.14	Myelodysplasia
22890	B937000	Refractory anaemia without sideroblasts, so stated
10817	B937100	Refractory anaemia with sideroblasts
23875	B937200	Refractory anaemia with excess of blasts
44420	B937300	Refractory anaemia with excess of blasts with transformation
11950	B937400	Essential (haemorrhagic) thrombocythaemia
12265	B937411	Primary thrombocythaemia
17386	B937500	Idiopathic thrombocythaemia
105985	B937600	Refractory anaemia without ring sideroblasts
106993	B937700	Refractory anaemia with ring sideroblasts
104740	B937800	Refractory anaemia with multilineage dysplasia
105915	B937900	5Q minus syndrome
105390	B937911	Myelodysplastic syndrome isolated del(5q) chromosomal abnorm
45285	B937W00	Myelodysplastic syndrome, unspecified
4561	B937W11	Myelodysplasia
19130	B937X00	Refractory anaemia, unspecified
21868	BB02.00	[M]Neoplasm, malignant
100590	BB03.12	[M]Tumour embolus
100112	BB03.13	[M]Tumour embolism
22267	BB04.00	[M]Neoplasm, malig, uncertain whether primary or metastatic
8627	BB07.00	[M]Tumour cells, malignant

22156	BB08.00	[M]Malignant tumour, small cell type
24511	BB09.00	[M]Malignant tumour, giant cell type
32213	BB0A.00	[M]Malignant tumour, fusiform cell type
20564	BB11.00	[M]Carcinoma in situ NOS
21914	BB11.11	[M]Intraepithelial carcinoma NOS
8695	BB12.00	[M]Carcinoma NOS
16692	BB14.00	[M]Carcinomatosis
57336	BB16.00	[M]Epithelioma, malignant
25961	BB17.00	[M]Large cell carcinoma NOS
21609	BB18.00	[M]Carcinoma, undifferentiated type, NOS
12609	BB19.00	[M]Carcinoma, anaplastic type, NOS
26413	BB1A.00	[M]Pleomorphic carcinoma
48048	BB1B.00	[M]Giant cell and spindle cell carcinoma
35474	BB1C.00	[M]Giant cell carcinoma
6966	BB1D.00	[M]Spindle cell carcinoma
54276	BB1E.00	[M]Pseudosarcomatous carcinoma
69300	BB1F.00	[M]Polygonal cell carcinoma
61984	BB1G.00	[M]Spheroidal cell carcinoma
9291	BB1J.00	[M]Small cell carcinoma NOS
66541	BB1J.12	[M]Round cell carcinoma
9156	BB1K.00	[M]Oat cell carcinoma
67970	BB1L.00	[M]Small cell carcinoma, fusiform cell type
30988	BB1M.00	[M]Small cell carcinoma, intermediate cell
21217	BB1N.00	[M]Small cell-large cell carcinoma
106519	BB1P.00	[M]Non-small cell carcinoma
38651	BB21.00	[M]Papillary carcinoma in situ
10541	BB22.00	[M]Papillary carcinoma NOS
34395	BB24.00	[M]Verrucous carcinoma NOS
43717	BB24.11	[M]Verrucous epidermoid carcinoma
20807	BB26.00	[M]Papillary squamous cell carcinoma
67912	BB26.11	[M]Papillary epidermoid carcinoma
10134	BB29.00	[M]Squamous cell carcinoma in situ NOS
19678	BB29.13	[M]Intraepithelial squamous cell carcinoma
1624	BB2A.00	[M]Squamous cell carcinoma NOS
24293	BB2B.00	[M]Squamous cell carcinoma, metastatic NOS
59143	BB2D.00	[M]Squamous cell carcinoma, large cell, non-keratinising
41816	BB2E.00	[M]Squamous cell carcinoma, small cell, non-keratinising
31004	BB2G.00	[M]Adenoid squamous cell carcinoma
61928	BB2H.00	[M]Squamous cell ca-in-situ, questionable stromal invasion
33497	BB2J.00	[M]Squamous cell carcinoma, microinvasive
45510	BB2M.00	[M]Lymphoepithelial carcinoma
44534	BB2N.00	[M]Intraepit neop,grade III,of cervix, vulva and vagina
21652	BB42.00	[M]Transitional cell carcinoma in situ
6436	BB43.00	[M]Transitional cell carcinoma NOS
12388	BB43.11	[M]Urothelial carcinoma
100111	BB46.00	[M]Schneiderian carcinoma

58798	BB47.00	[M]Transitional cell carcinoma, spindle cell type
38454	BB48.00	[M]Basaloid carcinoma
65216	BB49.00	[M]Cloacogenic carcinoma
9712	BB4A.00	[M]Papillary transitional cell carcinoma
101095	BB4B.00	[M]Grade 1 (Stage pTa) papillary urothelial/transit cell ca
102244	BB4C.00	[M]Grade 2 (Stage pTa) papillary urothelial/transit cell ca
101978	BB4D.00	[M]Grade 3 (Stage pTa) papillary urothelial/transit cell ca
33897	BB4z.00	[M]Transitional cell papilloma or carcinoma NOS
19091	BB5..00	[M]Adenomas and adenocarcinomas
2272	BB5..11	[M]Adenocarcinomas
27827	BB51.00	[M]Adenocarcinoma in situ
29170	BB51000	[M]Adenocarcinoma in situ in villous adenoma
37137	BB51100	[M]Adenocarcinoma in situ in tubulovillous adenoma
8930	BB52.00	[M]Adenocarcinoma NOS
44778	BB52000	[M]Adenocarcinoma in tubulovillous adenoma
5455	BB53.00	[M]Adenocarcinoma, metastatic, NOS
48223	BB54.00	[M]Scirrhous adenocarcinoma
27440	BB55.00	[M]Linitis plastica
71895	BB56.00	[M]Superficial spreading adenocarcinoma
28272	BB57.00	[M]Adenocarcinoma, intestinal type
59240	BB58.00	[M]Carcinoma, diffuse type
8101	BB5a.00	[M]Renal adenoma and carcinoma
10668	BB5a000	[M]Renal cell carcinoma
52266	BB5a011	[M]Grawitz tumour
15419	BB5a012	[M]Hypernephroma
34096	BB5b.00	[M]Granular cell carcinoma
8032	BB5B.00	[M]Pancreatic adenomas and carcinomas
11469	BB5B011	[M]Nesidioblastoma
63102	BB5B100	[M]Islet cell carcinoma
95609	BB5B300	[M]Insulinoma, malignant
32294	BB5B500	[M]Glucagonoma, malignant
98825	BB5B600	[M]Mixed islet cell and exocrine adenocarcinoma
4217	BB5c.00	[M]Parathyroid adenomas and adenocarcinomas
26858	BB5C.00	[M]Gastrinoma and carcinomas
35718	BB5C000	[M]Gastrinoma NOS
49629	BB5C100	[M]Gastrinoma, malignant
36031	BB5D.00	[M]Hepatobiliary tract adenomas and carcinomas
70516	BB5D.11	[M]Biliary tract adenomas and adenocarcinomas
8711	BB5D100	[M]Cholangiocarcinoma
40438	BB5D111	[M]Bile duct carcinoma
41313	BB5D300	[M]Bile duct cystadenocarcinoma
40240	BB5D500	[M]Hepatocellular carcinoma NOS
26814	BB5D512	[M]Hepatoma, malignant
25641	BB5D513	[M]Liver cell carcinoma
107299	BB5D700	[M]Combined hepatocellular carcinoma and cholangiocarcinoma
46771	BB5D800	[M]Hepatocellular carcinoma, fibrolamellar

98781	BB5F.00	[M]Trabecular adenocarcinoma
19263	BB5f.00	[M]Thyroid adenoma and adenocarcinoma
21741	BB5f100	[M]Follicular adenocarcinoma NOS
21847	BB5f111	[M]Follicular carcinoma
59918	BB5f200	[M]Follicular adenocarcinoma, well differentiated type
61467	BB5f300	[M]Follicular adenocarcinoma, trabecular type
46761	BB5f600	[M]Papillary and follicular adenocarcinoma
68757	BB5f700	[M]Nonencapsulated sclerosing carcinoma
60775	BB5h100	[M]Adrenal cortical carcinoma
33775	BB5J.00	[M]Adenoid cystic carcinoma
8606	BB5j.00	[M]Endometrioid adenomas and carcinomas
34879	BB5J.11	[M]Cylindroid adenocarcinoma
35747	BB5j100	[M]Endometrioid adenoma, borderline malignancy
9447	BB5j200	[M]Endometrioid carcinoma
99570	BB5j400	[M]Endometrioid adenofibroma, borderline malignancy
103034	BB5j500	[M]Endometrioid adenofibroma, malignant
50140	BB5K.00	[M]Cribriform carcinoma
18255	BB5L.00	[M]Adenomatous and adenocarcinomatous polyps
52326	BB5L100	[M]Adenocarcinoma in adenomatous polyp
55741	BB5L200	[M]Adenocarcinoma in situ in adenomatous polyp
73434	BB5L300	[M]Adenocarcinoma in multiple adenomatous polyps
6746	BB5M.00	[M]Tubular adenomas and adenocarcinomas
60045	BB5M100	[M]Tubular adenocarcinoma
41702	BB5N.00	[M]Adenomatous and adenocarcinomatous polyps of colon
73275	BB5N100	[M]Adenocarcinoma in adenomatous polposis coli
94083	BB5P.00	[M]Solid carcinoma NOS
34110	BB5R100	[M]Carcinoid tumour, malignant
100625	BB5R500	[M]Carcinoid tumour, nonargentaffin, malignant
55468	BB5R600	[M]Mucocarcinoid tumour, malignant
69210	BB5R611	[M]Goblet cell tumour
56794	BB5R800	[M]Adenocarcinoid tumour
26253	BB5R900	[M]Neuroendocrine carcinoma
26848	BB5S.00	[M]Respiratory tract adenomas and adenocarcinomas
34015	BB5S200	[M]Bronchiolo-alveolar adenocarcinoma
36530	BB5S211	[M]Alveolar cell carcinoma
16723	BB5S212	[M]Bronchiolar carcinoma
57802	BB5S400	[M]Alveolar adenocarcinoma
42273	BB5T.00	[M]Papillary adenomas and adenocarcinomas
35348	BB5T100	[M]Papillary adenocarcinoma NOS
6920	BB5U.00	[M]Villous adenomas and adenocarcinomas
67342	BB5U100	[M]Adenocarcinoma in villous adenoma
27849	BB5U200	[M]Villous adenocarcinoma
26120	BB5V.00	[M]Pituitary adenomas and carcinomas
68456	BB5V100	[M]Chromophobe carcinoma
36876	BB5V311	[M]Eosinophil carcinoma
72277	BB5V700	[M]Basophil carcinoma

40622	BB5V711	[M]Mucoid cell carcinoma
62199	BB5W.00	[M]Oxyphilic adenomas and adenocarcinomas
71497	BB5W100	[M]Oxyphilic adenocarcinoma
29008	BB5W111	[M]Hurthle cell adenocarcinoma
53129	BB5W112	[M]Oncytic adenocarcinoma
36882	BB5X.00	[M]Clear cell adenomas and adenocarcinomas
37354	BB5X100	[M]Clear cell adenocarcinoma NOS
27697	BB5Y.00	[M]Hypernephroid tumour
29362	BB5y.00	[M]Adenoma and adenocarcinoms OS
61764	BB5y100	[M]Vipoma
49900	BB5y200	[M]Klatskin's tumour
28625	BB71.00	[M]Mucoepidermoid carcinoma
34984	BB80.00	[M]Cystadenoma and carcinoma
34000	BB80100	[M]Cystadenocarcinoma NOS
69978	BB80200	[M]Borderline mucinous cystadenoma of the ovary
52263	BB81100	[M]Serous cystadenoma, borderline malignancy
38442	BB81200	[M]Serous cystadenocarcinoma, NOS
98696	BB81400	[M]Papillary cystadenoma, borderline malignancy
65051	BB81500	[M]Papillary cystadenocarcinoma, NOS
44930	BB81800	[M]Papillary serous cystadenocarcinoma
95774	BB81A00	[M]Serous surface papilloma, borderline malignancy
95150	BB81B00	[M]Serous surface papillary carcinoma
28396	BB81D00	[M]Mucinous cystadenoma, borderline malignancy
51656	BB81E00	[M]Mucinous cystadenocarcinoma NOS
66876	BB81E11	[M]Pseudomucinous adenocarcinoma
54749	BB81H00	[M]Papillary mucinous cystadenocarcinoma
21131	BB81J00	[M]Serous cystadenoma, borderline malignancy
46113	BB81K00	[M]Papillary cystadenoma, borderline malignancy
6203	BB81M00	[M]Papillary serous cystadenoma, borderline malignancy
40632	BB82.00	[M]Mucinous adenoma and adenocarcinoma
12497	BB82100	[M]Mucinous adenocarcinoma
30416	BB82111	[M]Colloid adenocarcinoma
95008	BB82112	[M]Gelatinous adenocarcinoma
55429	BB82113	[M]Mucoid adenocarcionoma
59284	BB82114	[M]Mucous adenocarcinoma
44074	BB84.00	[M]Mucin-producing adenocarcinoma
39038	BB85.00	[M]Signet ring carcinoma
61588	BB85000	[M]Signet ring cell carcinoma
54874	BB85100	[M]Metastatic signet ring cell carcinoma
53694	BB85111	[M]Krukenberg tumour
94438	BB85z00	[M]Signet ring carcinoma NOS
27728	BB90.00	[M]Intraductal carcinoma, noninfiltrating NOS
8351	BB91.00	[M]Infiltrating duct carcinoma
21833	BB91.11	[M]Duct carcinoma NOS
30189	BB91000	[M]Intraductal papillary adenocarcinoma with invasion
39760	BB91100	[M]Infiltrating duct and lobular carcinoma

62871	BB92.00	[M]Comedocarcinoma, noninfiltrating
58131	BB93.00	[M]Comedocarcinoma NOS
40359	BB94.00	[M]Juvenile breast carcinoma
67701	BB94.11	[M]Secretory breast carcinoma
102593	BB96.00	[M]Noninfiltrating intraductal papillary adenocarcinoma
16677	BB9B.00	[M]Medullary carcinoma NOS
47920	BB9B.11	[M]C cell carcinoma
50946	BB9C.00	[M]Medullary carcinoma with amyloid stroma
98883	BB9D.00	[M]Medullary carcinoma with lymphoid stroma
21861	BB9E.00	[M]Lobular carcinoma in situ
9956	BB9E000	[M]Intraductal carcinoma and lobular carcinoma in situ
12427	BB9F.00	[M]Lobular carcinoma NOS
7319	BB9G.00	[M]Infiltrating ductular carcinoma
32472	BB9H.00	[M]Inflammatory carcinoma
12300	BB9J.00	[M]Paget's disease, mammary
60803	BB9J.11	[M]Paget's disease, breast
42542	BB9K.00	[M]Paget's disease and infiltrating breast duct carcinoma
12480	BB9K000	[M]Paget's disease and intraductal carcinoma of breast
24523	BB9L.00	[M]Paget's disease, extramammary, exc Paget's disease bone
3969	BB9M.00	[M]Intracystic carcinoma NOS
28178	BBa0.00	[M]Craniopharyngioma
99949	BBa0.11	[M]Rathke's pouch tumour
37688	BBA2.00	[M]Acinar cell carcinoma
50151	BBa3.00	[M]Pineoblastoma
12309	BBb..00	[M]Gliomas
31574	BBb0.00	[M]Glioma, malignant
12580	BBB0.00	[M]Adenosquamous carcinoma
8523	BBb0.11	[M]Glioma NOS
34252	BBb0.12	[M]Gliosarcoma
38551	BBb1.00	[M]Gliomatosis cerebri
68808	BBb2.00	[M]Mixed glioma
16146	BBB2.00	[M]Adenocarcinoma with squamous metaplasia
39386	BBb2.11	[M]Mixed glioma
94267	BBb3.00	[M]Subependymal glioma
42553	BBB3.00	[M]Adenocarcinoma with cartilaginous and osseous metaplasia
90487	BBb3.11	[M]Subependymal astrocytoma NOS
28344	BBb3.12	[M]Subependymal astrocytoma NOS
50834	BBb3.13	[M]Subependymoma
49168	BBb4.00	[M]Subependymal giant cell astrocytoma
94810	BBB4.00	[M]Adenocarcinoma with spindle cell metaplasia
66000	BBB5.00	[M]Adenocarcinoma with apocrine metaplasia
59415	BBB6100	[M]Thymoma, malignant
20084	BBb7.00	[M]Ependymoma NOS
38770	BBB7.00	[M]Epithelial-myoepithelial carcinoma
52751	BBb8.00	[M]Ependymoma, anaplastic type
46769	BBb8.11	[M]Ependymoblastoma

70151	BBb9.00	[M]Papillary ependymoma
43114	BBbA.00	[M]Myxopapillary ependymoma
107884	BBba000	[M]Peripheral neuroectodermal tumour
8547	BBbB.00	[M]Astrocytoma NOS
27748	BBbB.11	[M]Astrocytic glioma
8328	BBbC.00	[M]Astrocytoma, anaplastic type
45531	BBbE.00	[M]Gemistocytic astrocytoma
27846	BBbF.00	[M]Fibrillary astrocytoma
30273	BBbG.00	[M]Pilocytic astrocytoma
61783	BBbG.11	[M]Juvenile astrocytoma
98800	BBbG.12	[M]Piloid astrocytoma
103047	BBbH.00	[M]Spongioblastoma NOS
50235	BBbK.00	[M]Astroblastoma
23083	BBbL.00	[M]Glioblastoma NOS
9575	BBbL.11	[M]Glioblastoma multiforme
66064	BBbM.00	[M]Giant cell glioblastoma
27744	BBbQ.00	[M]Oligodendroglioma NOS
49186	BBbR.00	[M]Oligodendroglioma, anaplastic type
46404	BBbS.00	[M]Oligodendroblastoma
34763	BBbT.00	[M]Medulloblastoma NOS
65952	BBbU.00	[M]Desmoplastic medulloblastoma
31767	BBbV.00	[M]Medullomyoblastoma
37473	BBbW.00	[M]Cerebellar sarcoma NOS
27653	BBbz.00	[M]Glioma NOS
67587	BBbZ.00	[M]Pleomorphic xanthoastrocytoma
107681	BBc3.00	[M]Teratoid medulloepithelioma
31609	BBC4.00	[M]Granulosa cell tumour, malignant
68479	BBc7.11	[M]Neuroastrocytoma
28836	BBc9.00	[M]Retinoblastomas
103883	BBc9100	[M]Retinoblastoma, undifferentiated type
48952	BBc9z00	[M]Retinoblastoma NOS
29580	BBCA.00	[M]Sertoli cell carcinoma
51878	BBcC.00	[M]Aesthesioneuroblastoma
39388	BBcC.11	[M]Olfactory neuroblastoma
95373	BBCC100	[M]Leydig cell tumour, malignant
95818	BBD1.00	[M]Paraganglioma, malignant
27363	BBd2.00	[M]Meningioma, malignant
60347	BBd2.11	[M]Leptomeningeal sarcoma
96798	BBd2.12	[M]Meningothelial sarcoma
65047	BBDA.00	[M]Phaeochromocytoma, malignant
106134	BBdB.00	[M]Meningeal sarcomatosis
50605	BBDB.00	[M]Glomangiosarcoma
105166	BBDB.11	[M]Glomoid sarcoma
7693	BBE..00	[M]Naevi and melanomas
579	BBE1.00	[M]Malignant melanoma NOS
24551	BBE1.11	[M]Melanocarcinoma

7483	BBE1.12	[M]Melanoma NOS
44157	BBE1.13	[M]Melanosarcoma NOS
67966	BBE1.14	[M]Naevocarcinoma
51353	BBE1000	[M]Malignant melanoma, regressing
58835	BBE1100	[M]Desmoplastic melanoma, malignant
20982	BBE2.00	[M]Nodular melanoma
62941	BBe2.00	[M]Neurofibrosarcoma
68889	BBE4.00	[M]Balloon cell melanoma
69981	BBe7.00	[M]Neurilemmoma, malignant
37477	BBe7.11	[M]Schwannoma, malignant
17292	BBE8.11	[M]Melanocytoma of eyeball
40492	BBe9.00	[M]Triton tumour, malignant
17232	BBEA.00	[M]Amelanotic melanoma
63574	BBEC.00	[M]Malignant melanoma in junctional naevus
43189	BBED.00	[M]Precancerous melanosis NOS
20709	BBEF.00	[M]Hutchinson's melanotic freckle
2705	BBEF.11	[M]Lentigo maligna
62088	BBEG.00	[M]Malignant melanoma in Hutchinson's melanotic freckle
11922	BBEG.11	[M]Lentigo maligna melanoma
22692	BBEG000	[M]Acral lentiginous melanoma, malignant
24208	BBEH.00	[M]Superficial spreading melanoma
73251	BBEM.00	[M]Malignant melanoma in giant pigmented naevus
23085	BBEP.00	[M]Epithelioid cell melanoma
44061	BBEQ.00	[M]Spindle cell melanoma NOS
92293	BBES.00	[M]Spindle cell melanoma, type B
40303	BBET.00	[M]Mixed epithelioid and spindle melanoma
68447	BBEV.00	[M]Blue naevus, malignant
39059	BBEX.00	[M]Melanoma in situ
41803	BBf..00	[M]Granular cell tumours and alveolar soft part sarcoma
17366	BBF..00	[M]Soft tissue tumours and sarcomas NOS
8085	BBF1.00	[M]Sarcoma NOS
34891	BBF2.00	[M]Sarcomatosis NOS
71869	BBf2.00	[M]Alveolar soft part sarcoma
31026	BBF3.00	[M]Spindle cell sarcoma
97463	BBF4.00	[M]Giant cell sarcoma (except of bone)
46581	BBF4.11	[M]Pleomorphic cell sarcoma
58837	BBF5.00	[M]Small cell sarcoma
69844	BBF5.11	[M]Round cell sarcoma
62396	BBF6.00	[M]Epithelioid cell sarcoma
55116	BBFz.00	[M]Soft tissue tumour or sarcoma NOS
17178	BBg..00	[M]Lymphomas, NOS or diffuse
36114	BBg1.00	[M]Malignant lymphoma NOS
31323	BBG1.00	[M]Fibrosarcoma NOS
1483	BBg1.11	[M]Lymphoma NOS
23711	BBg1000	[M]Malignant lymphoma, diffuse NOS
16460	BBg2.00	[M]Malignant lymphoma, non Hodgkin's type

3371	BBg2.11	[M]Non Hodgkins lymphoma
71117	BBg3.00	[M]Malignant lymphoma, undifferentiated cell type NOS
8088	BBG3.00	[M]Fibromyxosarcoma
46931	BBg4.00	[M]Malignant lymphoma, stem cell type
69301	BBg5.00	[M]Malignant lymphoma, convoluted cell type NOS
99655	BBg6.00	[M]Lymphosarcoma NOS
41754	BBg7.00	[M]Malignant lymphoma, lymphoplasmacytoid type
48253	BBg8.00	[M]Malignant lymphoma, immunoblastic type
95024	BBG8.00	[M]Infantile fibrosarcoma
94286	BBG8.11	[M]Congenital fibrosarcoma
68964	BBgA.00	[M]Malignant lymphoma, centroblastic-centrocytic, diffuse
41841	BBgB.00	[M]Malignant lymphoma, follicular centre cell NOS
69980	BBgC.00	[M]Malignant lymphoma, lymphocytic, well differentiated NOS
21463	BBgC.11	[M]Lymphocytic lymphoma NOS
60504	BBgC.12	[M]Lymphocytic lymphosarcoma NOS
51852	BBgD.00	[M]Malig lymphoma, lymphocytic, intermediate different NOS
39906	BBgE.00	[M]Malignant lymphoma, centrocytic
37680	BBGF.00	[M]Fibrous histiocytoma, malignant
72196	BBgG.00	[M]Malignant lymphoma, lymphocytic, poorly different NOS
67203	BBgG.11	[M]Lymphoblastic lymphosarcoma NOS
34352	BBgG.12	[M]Lymphoblastic lymphoma NOS
52591	BBgG.13	[M]Lymphoblastoma NOS
72241	BBgH.00	[M]Prolymphocytic lymphosarcoma
60275	BBgJ.00	[M]Malignant lymphoma, centroblastic type NOS
96231	BBGJ.00	[M]Fibroxanthoma, malignant
108682	BBgJ.11	[M]Germinoblastic sarcoma NOS
35034	BBGJ.11	[M]Fibroxanthosarcoma
66603	BBgK.00	[M]Malig lymphoma, follicular centre cell, non-cleaved NOS
46877	BBgL.00	[M]Malignant lymphoma, small lymphocytic NOS
31726	BBgM.00	[M]Malignant lymphoma, small cleaved cell, diffuse
31772	BBGM.00	[M]Dermatofibrosarcoma NOS
61251	BBgN.00	[M]Malign lymphoma,lymphocytic,intermediate differn, diffuse
71652	BBgP.00	[M]Malignant lymphoma, mixed small and large cell, diffuse
31090	BBGP.00	[M]Pigmented dermatofibrosarcoma protuberans
58015	BBgQ.00	[M]Malignant lymphomatous polyposis
33869	BBgR.00	[M]Malignant lymphoma, large cell, diffuse NOS
63994	BBgS.00	[M]Malignant lymphoma, large cell, cleaved, diffuse
71619	BBgT.00	[M]Malignant lymphoma, large cell, noncleaved, diffuse
51680	BBgV.00	[M]Malignant lymphoma, small cell, noncleaved, diffuse
51895	BBgz.00	[M]Lymphoma, diffuse or NOS
106137	BBh..00	[M]Reticulosarcomas
72433	BBh0.00	[M]Reticulosarcoma NOS
49825	BBh0.11	[M]Reticulum cell sarcoma NOS
21732	BBH1.00	[M]Myxosarcoma
100544	BBh2.00	[M]Reticulosarcoma, nodular
20710	BBj..00	[M]Hodgkin's disease

61997	BBj0.00	[M]Hodgkin's disease NOS
101429	BBj0.11	[M]Lymphogranuloma, malignant
56041	BBj1.00	[M]Hodgkin's disease, lymphocytic predominance
28599	BBJ1.00	[M]Liposarcoma NOS
101923	BBJ1.11	[M]Fibroliposarcoma
65584	BBj1000	[M]Hodgkin,s disease, lymphocytic predominance, diffuse
31537	BBj1100	[M]Hodgkin,s disease, lymphocytic predominance, nodular
51285	BBj2.00	[M]Hodgkin's disease, mixed cellularity
28628	BBJ3.00	[M]Liposarcoma, well differentiated type
96183	BBj4.00	[M]Hodgkin's disease,lymphocytic depletion,diffuse fibrosis
56676	BBJ5.00	[M]Myxoid liposarcoma
60127	BBJ5.12	[M]Myxoliposarcoma
42198	BBj6.00	[M]Hodgkin's disease, nodular sclerosis NOS
103708	BBJ6.00	[M]Round cell liposarcoma
40508	BBj6000	[M]Hodgkin,s disease, nodular sclerosis, lymphocytic predom
64343	BBj6100	[M]Hodgkin,s disease, nodular sclerosis, mixed cellularity
31741	BBj6200	[M]Hodgkin,s disease, nodular sclerosis, lymphocytic deplet
99200	BBj7.00	[M]Hodgkin's disease, nodular sclerosis, cellular phase
55947	BBJ7.00	[M]Pleomorphic liposarcoma
59651	BBJ8.00	[M]Mixed type liposarcoma
89230	BBj9.00	[M]Hodgkin's granuloma
7856	BBJH.00	[M]Dedifferentiated liposarcoma
42769	BBjz.00	[M]Hodgkin's disease NOS
20437	BBk..00	[M]Lymphomas, nodular or follicular
63699	BBk0.00	[M]Malignant lymphoma, nodular NOS
64947	BBk0.11	[M]Brill - Symmers' disease
27562	BBk0.12	[M]Follicular lymphosarcoma NOS
49253	BBk0.13	[M]Giant follicular lymphoma
10588	BBK0200	[M]Leiomyosarcoma NOS
56740	BBK0311	[M]Leiomyoblastoma
73916	BBK0400	[M]Epithelioid leiomyosarcoma
64596	BBK0700	[M]Myxoid leiomyosarcoma
67019	BBK1100	[M]Angiomyosarcoma
98961	BBk2.00	[M]Malignant lymphoma, centroblastic-centrocytic, follicular
31818	BBK2.00	[M]Myoma and myosarcoma
55268	BBK2100	[M]Myosarcoma
106970	BBk3.00	[M]Malig lymphoma, lymphocytic, well differentiated,nodular
31421	BBK3100	[M]Rhabdomyosarcoma NOS
57505	BBK3200	[M]Pleomorphic rhabdomyosarcoma
105944	BBK3300	[M]Mixed cell rhabdomyosarcoma
48275	BBK3600	[M]Embryonal rhabdomyosarcoma
63247	BBK3611	[M]Sarcoma botryoides
42082	BBK3700	[M]Alveolar rhabdomyosarcoma
39883	BBk5.00	[M]Malig lymp, follicular centre cell, cleaved, follicular
97852	BBk7.00	[M]Malignant lymphoma, centroblastic type, follicular
58953	BBk8.00	[M]Malig lymp,follicular centre cell,noncleaved,follicular

40513	BBkz.00	[M]Lymphoma, nodular or follicular NOS
46967	BBl..00	[M]Mycosis fungoides
95464	BBl0.00	[M]Mycosis fungoides
34030	BBL0.00	[M]Endometrial stromal sarcoma
97756	BBl1.00	[M]Sezary's disease
66607	BBL4.00	[M]Mixed tumour, malignant, NOS
71161	BBL7.00	[M]Mixed and stromal renal neoplasms
43703	BBL7.11	[M]Nephromas and nephroblastomas
54594	BBL7000	[M]Mesoblastic nephroma
21681	BBL7100	[M]Nephroblastoma NOS
36870	BBL7111	[M]Adenosarcoma
17314	BBL7112	[M]Wilms' tumour
100371	BBL7200	[M]Epithelial nephroblastoma
105862	BBL7300	[M]Mesenchymal nephroblastoma
57677	BBL8.00	[M]Hepatoblastoma
106889	BBL8.11	[M]Embryonal hepatoma
19334	BBL9.00	[M]Carcinosarcoma NOS
67934	BBLA.00	[M]Carcinosarcoma, embryonal type
61082	BBLA.11	[M]Pneumoblastoma
87003	BBLC100	[M]Mesenchymoma, malignant
98797	BBLD.00	[M]Embryonal sarcoma
63518	BBLE.00	[M]Adenosarcoma
37510	BBLG.00	[M]Carcinoma in pleomorphic adenoma
17212	BBLH.00	[M]Rhabdoid sarcoma
18771	BBLJ.00	[M]Clear cell sarcoma of kidney
48348	BBLM.00	[M]Pulmonary blastoma
99695	BBlz.00	[M]Mycosis fungoides NOS
63973	BBm0.00	[M]Microglioma
71490	BBM0000	[M]Brenner tumour, borderline malignancy
70383	BBM0100	[M]Brenner tumour, malignant
63239	BBm1.00	[M]Malignant histiocytosis
70740	BBm1.11	[M]Malignant reticulosis
59593	BBm3.00	[M]Letterer - Siwe disease
45768	BBm3.12	[M]Acute progressive histiocytosis X
57544	BBm4.00	[M]True histiocytic lymphoma
40766	BBm5.00	[M] Peripheral T-cell lymphoma NOS
39312	BBM8.00	[M]Cystosarcoma phyllodes NOS
31492	BBm9.00	[M] Monocytoid B-cell lymphoma
59251	BBM9.00	[M]Cystosarcoma phyllodes, malignant
56756	BBmA.00	[M] Refractory anaemia with sideroblasts
60186	BBmB.00	[M]Refractory anaemia+excess of blasts with transformation
49530	BBmC.00	[M] T-gamma lymphoproliferative disease
16774	BBmD.00	[M] Cutaneous lymphoma
52593	BBmE.00	[M] Gamma heavy chain disease
61146	BBmF.00	[M] Angiocentric immunoproliferative lesion
18383	BBmH.00	[M] Large cell lymphoma

68353	BBmJ.00	[M] Angioendotheliomatosis
9172	BBmK.00	[M]Waldenstrom's macroglobulinaemia
94921	BBmL.00	[M] Refractory anaemia with excess of blasts
31671	BBn0.00	[M]Plasma cell myeloma
18744	BBn0.11	[M]Multiple myeloma
3672	BBn0.12	[M]Myeloma NOS
53647	BBn0.13	[M]Myelomatosis
39490	BBn0.14	[M]Plasmacytic myeloma
50379	BBN1.00	[M]Synovial sarcoma NOS
105073	BBN2.00	[M]Synovial sarcoma, spindle cell type
99702	BBn3.00	[M]Plasma cell tumour, malignant
57796	BBN4.00	[M]Synovial sarcoma, biphasic type
63286	BBN5.00	[M]Clear cell sarcoma of tendons and aponeuroses
94239	BBp1.00	[M]Mast cell sarcoma
27509	BBP1.00	[M]Mesothelioma, malignant
67339	BBp2.00	[M]Malignant mastocytosis
104720	BBP3.11	[M]Sarcomatoid mesothelioma
47734	BBP5.00	[M]Epithelioid mesothelioma, malignant
86820	BBP7.00	[M]Mesothelioma, biphasic type, malignant
21770	BBPX.00	[M]Mesothelioma, unspecified
7476	BBQ1.00	[M]Seminomas
57084	BBQ1000	[M]Seminoma, anaplastic type
35223	BBQ1100	[M]Spermatocytic seminoma
9859	BBQ1z00	[M]Seminoma NOS
28941	BBQ3.00	[M]Embryonal carcinoma NOS
37621	BBQ4.00	[M]Endodermal sinus tumour
104147	BBQ4.11	[M]Infantile embryonal carcinoma
55658	BBQ4.12	[M]Orchioblastoma
20350	BBQ4.14	[M]Yolk sac tumour
40449	BBQ6.00	[M]Gonadoblastoma
33636	BBQ7200	[M]Teratoma, malignant, NOS
57087	BBQ7211	[M]Embryonal teratoma
43865	BBQ7212	[M]Immature teratoma
52493	BBQ7213	[M]Teratoblastoma, malignant
37542	BBQ7300	[M]Teratocarcinoma
61542	BBQ7400	[M]Malignant teratoma, undifferentiated type
21682	BBQ7500	[M]Malignant teratoma, intermediate type
65861	BBQ9.00	[M]Dermoid cyst with malignant transformation
71301	BBQA100	[M]Struma ovarii, malignant
4637	BBr..00	[M]Leukaemias
40420	BBr0.00	[M]Leukaemias unspecified
41734	BBr0000	[M]Leukaemia NOS
6316	BBr0100	[M]Acute leukaemia NOS
22071	BBr0111	[M]Blast cell leukaemia
64963	BBr0112	[M]Blastic leukaemia
63570	BBr0113	[M]Stem cell leukaemia

72179	BBr0200	[M]Subacute leukaemia NOS
31750	BBr0300	[M]Chronic leukaemia NOS
72310	BBr0400	[M]Aleukaemic leukaemia NOS
59929	BBr0z00	[M]Leukaemia unspecified, NOS
59409	BBR1.00	[M]Invasive hydatidiform mole
56538	BBR1.11	[M]Chorioadenoma
68211	BBR1.12	[M]Chorioadenoma destruens
47339	BBR1.13	[M]Invasive mole NOS
48155	BBr2.00	[M]Lymphoid leukaemias
67712	BBR2.00	[M]Choriocarcinoma
12146	BBr2000	[M]Lymphoid leukaemia NOS
20635	BBr2011	[M]Lymphatic leukaemia
37410	BBr2100	[M]Acute lymphoid leukaemia
41500	BBr2300	[M]Chronic lymphoid leukaemia
46048	BBr2500	[M]Prolymphocytic leukaemia
50928	BBr2600	[M]Burkitt's cell leukaemia
29335	BBr2700	[M]Adult T-cell leukaemia/lymphoma
64618	BBr3.00	[M]Plasma cell leukaemias
54627	BBR3.00	[M]Choriocarcinoma combined with teratoma
46444	BBr4.00	[M]Erythroleukaemias
29945	BBR4.00	[M]Malignant teratoma, trophoblastic
70935	BBr4000	[M]Erythroleukaemia
100927	BBr4z00	[M]Erythroleukaemia NOS
4873	BBR5.00	[M]Partial hydatidiform mole
35697	BBr6.00	[M]Myeloid leukaemias
88593	BBR6.00	[M]Placental site trophoblastic tumour
71850	BBr6000	[M]Myeloid leukaemia NOS
37723	BBr6011	[M]Granulocytic leukaemia NOS
54585	BBr6100	[M]Acute myeloid leukaemia
106483	BBr6200	[M]Subacute myeloid leukaemia
52942	BBr6300	[M]Chronic myeloid leukaemia
66694	BBr6311	[M]Naegeli-type monocytic leukaemia
57316	BBr6600	[M]Acute promyelocytic leukaemia
46263	BBr6700	[M]Acute myelomonocytic leukaemia
48049	BBr6800	[M]Chronic myelomonocytic leukaemia
108964	BBr6900	[M]Juvenile myelomonocytic leukaemia
62330	BBr6z00	[M]Other myeloid leukaemia NOS
28635	BBR7.00	[M]Classical hydatidiform mole
106197	BBr7000	[M]Basophilic leukaemia
57713	BBr8.00	[M]Eosinophilic leukaemias
47989	BBR8.00	[M]Complete hydatidiform mole
71377	BBr8000	[M]Eosinophilic leukaemia
107773	BBr8z00	[M]Eosinophilic leukaemia NOS
73088	BBr9000	[M]Monocytic leukaemia NOS
73066	BBrA.00	[M]Miscellaneous leukaemias
72222	BBrA100	[M]Megakaryocytic leukaemia

69299	BBrA111	[M]Thrombocytic leukaemia
96893	BBrA300	[M]Myeloid sarcoma
93944	BBrA311	[M]Chloroma
98009	BBrA312	[M]Granulocytic sarcoma
5915	BBrA400	[M]Hairy cell leukaemia
49327	BBrA500	[M]Acute megakaryoblastic leukaemia
102764	BBrA600	[M]Acute panmyelosis
37487	BBrA700	[M]Acute myelofibrosis
108316	BBrAz00	[M]Miscellaneous leukaemia NOS
42297	BBrz.00	[M]Leukaemia NOS
96078	BBRz.00	[M]Trophoblastic neoplasm NOS
69462	BBS..00	[M]Mesonephromas
30139	BBs..00	[M]Misc myeloproliferative and lymphoproliferative disorders
16922	BBs0.00	[M]Polycythaemia vera
58888	BBs0.11	[M]Polycythaemia rubra vera
101271	BBs1.00	[M]Acute panmyelosis
17091	BBs2.00	[M]Chronic myeloproliferative disease
30043	BBs4.00	[M]Idiopathic thrombocythaemia
9673	BBs5.00	[M]Chronic lymphoproliferative disease
37692	BBsz.00	[M]Misc myeloproliferative or lymphoproliferative dis NOS
62348	BBT1.00	[M]Haemangiosarcoma
22650	BBT1.11	[M]Angiosarcoma
98322	BBT7100	[M]Haemangioendothelioma, malignant
27439	BBTA.00	[M]Kaposi's sarcoma
105296	BBTD200	[M]Haemangiopericytoma, malignant
38481	BBTK.00	[M]Epithelioid haemangioendothelioma, malignant
57729	BBU1.00	[M]Lymphangiosarcoma
39522	BBV..00	[M]Osteomas and osteosarcomas
7799	BBv..00	[M]Myelodysplastic syndrome
99665	BBV..11	[M]Juxtacortical osteogenic sarcoma
63571	BBV..12	[M]Parosteal osteosarcoma
105275	BBV..13	[M]Periosteal osteogenic sarcoma
31749	BBv0.00	[M]Monocytoid B-cell lymphoma
8660	BBV1.00	[M]Osteosarcoma NOS
49862	BBV1.11	[M]Osteoblastic sarcoma
59310	BBV1.12	[M]Osteochondrosarcoma
5052	BBV1.13	[M]Osteogenic sarcoma NOS
24539	BBV2.00	[M]Chondroblastic osteosarcoma
27965	BBv2.00	[M]AngiocentricT-cell lymphoma
21447	BBV3.00	[M]Fibroblastic osteosarcoma
22561	BBV4.00	[M]Telangiectatic osteosarcoma
60631	BBV5.00	[M]Osteosarcoma in Paget's disease of bone
4118	BBV9.00	[M]Myxoid chondrosarcoma
29337	BBVA.00	[M] Small cell osteosarcoma
7941	BBW4.00	[M]Chondrosarcoma NOS
68220	BBW4.11	[M]Fibrochondrosarcoma

63659	BBW6.00	[M]Juxtacortical chondrosarcoma
98559	BBW8.00	[M]Chondroblastoma, malignant
52684	BBW9.00	[M]Mesenchymal chondrosarcoma
68956	BBX1.00	[M]Giant cell tumour of bone, malignant
50859	BBX1.11	[M]Giant cell bone sarcoma
31673	BBX1.12	[M]Osteoclastoma, malignant
99797	BBX3.00	[M]Malignant giant cell tumour of soft parts
4473	BBY0.00	[M]Ewing's sarcoma
49023	BBY0.11	[M]Endothelial bone sarcoma
72443	BBZ2.00	[M]Odontogenic tumour, malignant
93175	BBZ2.11	[M]Intraosseous carcinoma
46741	BBZC.00	[M]Ameloblastic odontosarcoma
97593	BBZG.00	[M]Ameloblastoma, malignant
100267	BBZG.11	[M]Adamantinoma, malignant
68730	BBZN.00	[M]Ameloblastic fibrosarcoma
98483	BBZN.11	[M]Odontogenic fibrosarcoma
58973	Byu0.00	[X]Malignant neoplasm of lip, oral cavity and pharynx
35180	Byu1.00	[X]Malignant neoplasm of digestive organs
43490	Byu1100	[X]Other specified carcinomas of liver
45766	Byu1200	[X]Malignant neoplasm of intestinal tract, part unspecified
49292	Byu1300	[X]Malignant neoplsm/ill-defin sites within digestive system
35325	Byu2.00	[X]Malignant neoplasm of respiratory and intrathoracic orga
40595	Byu2000	[X]Malignant neoplasm of bronchus or lung, unspecified
66444	Byu2100	[X]Malignant neoplasm/overlap lesion/heart,mediastinm+pleura
99096	Byu2300	[X]Malignant neopl/overlapping les/resp+intrathoracic organs
86997	Byu2400	[X]Malignant neoplasm/ill-defined sites within resp system
50292	Byu2500	[X]Malignant neoplasm of mediastinum, part unspecified
40749	Byu3.00	[X]Malignant neoplasm of bone and articular cartilage
73296	Byu3100	[X]Malignant neoplasm/bones+articular cartilage/limb,unspfd
63300	Byu3200	[X]Malignant neoplasm/overlap lesion/bone+articulr cartilage
43151	Byu3300	[X]Malignant neoplasm/bone+articular cartilage, unspecified
56925	Byu4000	[X]Malignant melanoma of other+unspecified parts of face
19444	Byu4100	[X]Malignant melanoma of skin, unspecified
40592	Byu5.00	[X]Malignant neoplasm of mesothelial and soft tissue
67034	Byu5000	[X]Mesothelioma of other sites
21715	Byu5011	[X]Mesothelioma of lung
30526	Byu5100	[X]Mesothelioma, unspecified
93665	Byu5300	[X]Kaposi's sarcoma, unspecified
101668	Byu5400	[X]Malignant neoplasm/peripheral nerves of trunk,unspecified
105072	Byu5500	[X]Mal neoplasm/overlap les/periph nerv+autonomic nerv systm
95671	Byu5700	[X]Malignant neoplasm of peritoneum, unspecified
91896	Byu5800	[X]Mal neoplasm/connective+soft tissue of trunk,unspecified
91457	Byu5900	[X]Malignant neoplasm/connective + soft tissue,unspecified
98361	Byu5B00	[X]Kaposi's sarcoma of other sites
12499	Byu6.00	[X]Malignant neoplasm of breast
40598	Byu7.00	[X]Malignant neoplasm of female genital organs

64497	Byu7000	[X]Malignant neoplasm of uterine adnexa, unspecified
57756	Byu7100	[X]Malignant neoplasm/other specified female genital organs
55588	Byu7300	[X]Malignant neoplasm of female genital organ, unspecified
40671	Byu8.00	[X]Malignant neoplasm of male genital organs
57191	Byu8000	[X]Malignant neoplasm/other specified male genital organs
45262	Byu8200	[X]Malignant neoplasm of male genital organ, unspecified
35113	Byu9.00	[X]Malignant neoplasm of urinary tract
45260	Byu9000	[X]Malignant neoplasm of urinary organ, unspecified
35285	ByuA.00	[X]Malignant neoplasm of eye, brain and other parts of cent
68027	ByuA000	[X]Malignant neoplasm/other and unspecified cranial nerves
41515	ByuA100	[X]Malignant neoplasm/central nervous system, unspecified
63925	ByuA200	[X]Malignant neoplasm of meninges, unspecified
47633	ByuA300	[X]Malig neopl, overlap lesion brain & other part of CNS
40608	ByuB.00	[X]Malignant neoplasm of thyroid and other endocrine glands
64309	ByuB100	[X]Malignant neoplasm of endocrine gland, unspecified
35186	ByuC.00	[X]Malignant neoplasm of ill-defined, secondary and unspeci
39027	ByuC000	[X]Malignant neoplasm of other specified sites
96226	ByuC100	[X]Malignant neoplasm/overlap lesion/other+ill-defined sites
52029	ByuC800	[X]Malignant neoplasm without specification of site
40740	ByuD.00	[X]Malignant neoplasms of lymphoid, haematopoietic and rela
43415	ByuD000	[X]Other Hodgkin's disease
67518	ByuD100	[X]Other types of follicular non-Hodgkin's lymphoma
98596	ByuD200	[X]Other types of diffuse non-Hodgkin's lymphoma
64336	ByuD300	[X]Other specified types of non-Hodgkin's lymphoma
102688	ByuD400	[X]Other malignant immunoproliferative diseases
67029	ByuD500	[X]Other lymphoid leukaemia
61693	ByuD600	[X]Other myeloid leukaemia
89762	ByuD700	[X]Other monocytic leukaemia
89329	ByuD800	[X]Other specified leukaemias
65165	ByuD900	[X]Other leukaemia of unspecified cell type
105025	ByuDA00	[X]Oth spcf mal neoplsm/lymphoid,haematopoietic+rltd tissue
72500	ByuDB00	[X]Mal neoplasm/lymphoid,haematopoietic+related tissu,unspcf
64515	ByuDC00	[X]Diffuse non-Hodgkin's lymphoma, unspecified
63375	ByuDE00	[X]Unspecified B-cell non-Hodgkin's lymphoma
8649	ByuDF00	[X]Non-Hodgkin's lymphoma, unspecified type
7940	ByuDF11	[X]Non-Hodgkin's lymphoma NOS
63598	ByuE.00	[X]Malignant neoplasms/independent (primary) multiple sites
64897	ByuE000	[X]Malignant neoplasms/independent(primary)multiple sites
101772	ByuF.00	[X]In situ neoplasms
102708	ByuF100	[X]Carcinoma in situ of other specified digestive organs
100781	ByuF300	[X]Carcinoma in situ of other parts of respiratory system
97628	ByuF600	[X]Melanoma in situ of other sites
72695	ByuFA00	[X]Carcinoma in situ of other parts of cervix
106003	ByuFC00	[X]Carcinoma in situ of oth+unspecified male genital organs
73261	ByuFF00	[X]Melanoma in situ, unspecified
53803	ByuFG00	[X]Other carcinoma in situ of breast

45143	ByuHD00	[X]Myelodysplastic syndrome, unspecified
30537	F373.00	Polyneuropathy in malignant disease
57551	F381100	Myasthenic syndrome due to other malignancy
49482	F396200	Myopathy due to malignant disease
7593	H51y700	Malignant pleural effusion
108591	K01w100	Drash syndrome
108922	K01w112	Wilms' tumour + nephrotic syndrome + pseudohermaphroditism
60433	N330900	Osteoporosis in multiple myelomatosis
41577	1477	H/O: cerebrovascular disease
31941	A94y600	Rupture of syphilitic cerebral aneurysm
25114	E030400	Acute confusional state, of cerebrovascular origin
24035	E031400	Subacute confusional state, of cerebrovascular origin
54744	F11x200	Cerebral degeneration due to cerebrovascular disease
1195	F423600	Amaurosis fugax
50242	F423700	Retinal transient arterial occlusion NOS
39309	F481400	Other transient visual loss
63746	Fyu5500	[X]Other transnt cerebral ischaemic attacks+related syndroms
95347	Fyu5700	[X]Other vascular syndroms/brain in cerebrovasculr diseases
2418	G6...00	Cerebrovascular disease
1786	G60..00	Subarachnoid haemorrhage
29939	G600.00	Ruptured berry aneurysm
56007	G601.00	Subarachnoid haemorrhage from carotid siphon and bifurcation
19412	G602.00	Subarachnoid haemorrhage from middle cerebral artery
42331	G603.00	Subarachnoid haemorrhage from anterior communicating artery
9696	G604.00	Subarachnoid haemorrhage from posterior communicating artery
41910	G605.00	Subarachnoid haemorrhage from basilar artery
60692	G606.00	Subarachnoid haemorrhage from vertebral artery
17326	G60X.00	Subarachnoid haemorrh from intracranial artery, unspecif
23580	G60z.00	Subarachnoid haemorrhage NOS
5051	G61..00	Intracerebral haemorrhage
6960	G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
18604	G61..12	Stroke due to intracerebral haemorrhage
31595	G610.00	Cortical haemorrhage
40338	G611.00	Internal capsule haemorrhage
46316	G612.00	Basal nucleus haemorrhage
13564	G613.00	Cerebellar haemorrhage
7912	G614.00	Pontine haemorrhage
62342	G615.00	Bulbar haemorrhage
30045	G616.00	External capsule haemorrhage
30202	G617.00	Intracerebral haemorrhage, intraventricular
57315	G618.00	Intracerebral haemorrhage, multiple localized
107440	G619.00	Lobar cerebral haemorrhage
31060	G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
28314	G61X000	Left sided intracerebral haemorrhage, unspecified
19201	G61X100	Right sided intracerebral haemorrhage, unspecified
3535	G61z.00	Intracerebral haemorrhage NOS

31805	G62..00	Other and unspecified intracranial haemorrhage
36178	G620.00	Extradural haemorrhage - nontraumatic
4273	G621.00	Subdural haemorrhage - nontraumatic
17734	G622.00	Subdural haematoma - nontraumatic
18912	G623.00	Subdural haemorrhage NOS
20284	G62z.00	Intracranial haemorrhage NOS
45781	G63..00	Precerebral arterial occlusion
57495	G63..11	Infarction - precerebral
63830	G63..12	Stenosis of precerebral arteries
32447	G630.00	Basilar artery occlusion
4240	G631.00	Carotid artery occlusion
2156	G631.11	Stenosis, carotid artery
4152	G631.12	Thrombosis, carotid artery
40847	G632.00	Vertebral artery occlusion
98642	G633.00	Multiple and bilateral precerebral arterial occlusion
2652	G634.00	Carotid artery stenosis
51326	G63y.00	Other precerebral artery occlusion
23671	G63y000	Cerebral infarct due to thrombosis of precerebral arteries
24446	G63y100	Cerebral infarction due to embolism of precerebral arteries
71585	G63z.00	Precerebral artery occlusion NOS
8837	G64..00	Cerebral arterial occlusion
5363	G64..11	CVA - cerebral artery occlusion
569	G64..12	Infarction - cerebral
6155	G64..13	Stroke due to cerebral arterial occlusion
16517	G640.00	Cerebral thrombosis
36717	G640000	Cerebral infarction due to thrombosis of cerebral arteries
15019	G641.00	Cerebral embolism
34758	G641.11	Cerebral embolus
27975	G641000	Cerebral infarction due to embolism of cerebral arteries
3149	G64z.00	Cerebral infarction NOS
15252	G64z.11	Brainstem infarction NOS
5602	G64z.12	Cerebellar infarction
25615	G64z000	Brainstem infarction
47642	G64z100	Wallenberg syndrome
5185	G64z111	Lateral medullary syndrome
9985	G64z200	Left sided cerebral infarction
10504	G64z300	Right sided cerebral infarction
26424	G64z400	Infarction of basal ganglia
504	G65..00	Transient cerebral ischaemia
3132	G65..11	Drop attack
1433	G65..12	Transient ischaemic attack
2417	G65..13	Vertebro-basilar insufficiency
23942	G650.00	Basilar artery syndrome
5268	G650.11	Insufficiency - basilar artery
33377	G651.00	Vertebral artery syndrome
21118	G651000	Vertebro-basilar artery syndrome

23465	G652.00	Subclavian steal syndrome
44765	G653.00	Carotid artery syndrome hemispheric
50594	G654.00	Multiple and bilateral precerebral artery syndromes
6489	G655.00	Transient global amnesia
10794	G656.00	Vertebrobasilar insufficiency
105738	G657.00	Carotid territory transient ischaemic attack
19354	G65y.00	Other transient cerebral ischaemia
1895	G65z.00	Transient cerebral ischaemia NOS
55247	G65z000	Impending cerebral ischaemia
16507	G65z100	Intermittent cerebral ischaemia
15788	G65zz00	Transient cerebral ischaemia NOS
1469	G66..00	Stroke and cerebrovascular accident unspecified
1298	G66..11	CVA unspecified
6253	G66..12	Stroke unspecified
6116	G66..13	CVA - Cerebrovascular accident unspecified
18689	G660.00	Middle cerebral artery syndrome
19280	G661.00	Anterior cerebral artery syndrome
19260	G662.00	Posterior cerebral artery syndrome
8443	G663.00	Brain stem stroke syndrome
17322	G664.00	Cerebellar stroke syndrome
33499	G665.00	Pure motor lacunar syndrome
51767	G666.00	Pure sensory lacunar syndrome
7780	G667.00	Left sided CVA
12833	G668.00	Right sided CVA
16956	G669.00	Cerebral palsy, not congenital or infantile, acute
13577	G67..00	Other cerebrovascular disease
11171	G670.00	Cerebral atherosclerosis
5184	G670.11	Precerebral atherosclerosis
40053	G671.00	Generalised ischaemic cerebrovascular disease NOS
70536	G671000	Acute cerebrovascular insufficiency NOS
24385	G671100	Chronic cerebral ischaemia
12555	G671z00	Generalised ischaemic cerebrovascular disease NOS
4635	G673.00	Cerebral aneurysm, nonruptured
22018	G673000	Dissection of cerebral arteries, nonruptured
35059	G673100	Carotico-cavernous sinus fistula
12634	G673200	Carotid artery dissection
97122	G673300	Vertebral artery dissection
22400	G674.00	Cerebral arteritis
10189	G674000	Cerebral amyloid angiopathy
32310	G675.00	Moyamoya disease
37947	G676.00	Nonpyogenic venous sinus thrombosis
39344	G676000	Cereb infarct due cerebral venous thrombosis, nonpyogenic
31704	G677.00	Occlusion/stenosis cerebral arts not result cerebral infarct
51759	G677000	Occlusion and stenosis of middle cerebral artery
57527	G677100	Occlusion and stenosis of anterior cerebral artery
65770	G677200	Occlusion and stenosis of posterior cerebral artery

55602	G677300	Occlusion and stenosis of cerebellar arteries
71274	G677400	Occlusion+stenosis of multiple and bilat cerebral arteries
9943	G678.00	Cereb autosom dominant arteriop subcort infarcts leukoenceph
98188	G679.00	Small vessel cerebrovascular disease
101733	G67A.00	Cerebral vein thrombosis
34117	G67y.00	Other cerebrovascular disease OS
37493	G67z.00	Other cerebrovascular disease NOS
23361	G68..00	Late effects of cerebrovascular disease
44740	G680.00	Sequelae of subarachnoid haemorrhage
48149	G681.00	Sequelae of intracerebral haemorrhage
43451	G682.00	Sequelae of other nontraumatic intracranial haemorrhage
39403	G683.00	Sequelae of cerebral infarction
51138	G68W.00	Sequelae/other + unspecified cerebrovascular diseases
6228	G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction
40758	G6W..00	Cereb infarct due unsp occlus/stenos precerebr arteries
33543	G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
51311	G6y..00	Other specified cerebrovascular disease
10062	G6z..00	Cerebrovascular disease NOS
73901	Gyu6.00	[X]Cerebrovascular diseases
108668	Gyu6000	[X]Subarachnoid haemorrhage from other intracranial arteries
65745	Gyu6100	[X]Other subarachnoid haemorrhage
53810	Gyu6200	[X]Other intracerebral haemorrhage
91627	Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
53745	Gyu6400	[X]Other cerebral infarction
90572	Gyu6500	[X]Occlusion and stenosis of other precerebral arteries
92036	Gyu6600	[X]Occlusion and stenosis of other cerebral arteries
99367	Gyu6A00	[X]Other cerebrovascular disorders in diseases CE
108630	Gyu6E00	[X]Subarachnoid haemorrh from intracranial artery, unspecif
96630	Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
94482	Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
42335	L440.00	Cerebrovascular disorders in the puerperium
47607	L440.11	CVA - cerebrovascular accident in the puerperium
56279	L440.12	Stroke in the puerperium
67640	L440000	Puerperal cerebrovascular disorder unspecified
97470	L440100	Puerperal cerebrovascular disorder - delivered
91272	L440300	Puerperal cerebrovascular disorder with antenatal comp
3608	R014.00	[D]Transient paralysis of a limb
29657	R014000	[D]Transient monoplegia NOS
41513	R014z00	[D]Transient limb paralysis NOS
19348	ZV12511	[V]Personal history of stroke
7138	ZV12512	[V]Personal history of cerebrovascular accident (CVA)
101251	ZV12D00	[V]Personal history of transient ischaemic attack
5867	173A.00	Exercise induced asthma
22752	173c.00	Occupational asthma
73522	173d.00	Work aggravated asthma
11022	178..00	Asthma trigger

41017	1780	Aspirin induced asthma
102341	1781	Asthma trigger - pollen
103955	1782	Asthma trigger - tobacco smoke
102952	1783	Asthma trigger - warm air
103952	1784	Asthma trigger - emotion
103945	1785	Asthma trigger - damp
103321	1786	Asthma trigger - animals
102301	1787	Asthma trigger - seasonal
103813	1788	Asthma trigger - cold air
102449	1789	Asthma trigger - respiratory infection
103944	178A.00	Asthma trigger - airborne dust
102871	178B.00	Asthma trigger - exercise
11370	1O2..00	Asthma confirmed
24479	663d.00	Emergency asthma admission since last appointment
25181	663e.00	Asthma restricts exercise
26861	6.63E+02	Asthma sometimes restricts exercise
26506	6.63E+102	Asthma severely restricts exercise
26504	663f.00	Asthma never restricts exercise
13066	663h.00	Asthma - currently dormant
10487	663j.00	Asthma - currently active
47337	663m.00	Asthma accident and emergency attendance since last visit
19520	663n.00	Asthma treatment compliance satisfactory
7416	663N.00	Asthma disturbing sleep
30815	663N000	Asthma causing night waking
38146	663N100	Asthma disturbs sleep weekly
13175	663N200	Asthma disturbs sleep frequently
13173	663O.00	Asthma not disturbing sleep
38143	663O000	Asthma never disturbs sleep
19519	663p.00	Asthma treatment compliance unsatisfactory
7191	663P.00	Asthma limiting activities
102713	663P000	Asthma limits activities 1 to 2 times per month
102888	663P100	Asthma limits activities 1 to 2 times per week
103998	663P200	Asthma limits activities most days
13174	663Q.00	Asthma not limiting activities
42824	663q.00	Asthma daytime symptoms
39570	663r.00	Asthma causes night symptoms 1 to 2 times per month
26501	663s.00	Asthma never causes daytime symptoms
31225	663t.00	Asthma causes daytime symptoms 1 to 2 times per month
24884	663u.00	Asthma causes daytime symptoms 1 to 2 times per week
7378	663U.00	Asthma management plan given
13064	663V.00	Asthma severity
26503	663v.00	Asthma causes daytime symptoms most days
3458	663V000	Occasional asthma
3018	663V100	Mild asthma
13065	663V200	Moderate asthma
3366	663V300	Severe asthma

38144	663w.00	Asthma limits walking up hills or stairs
7229	663W.00	Asthma prophylactic medication used
38145	663x.00	Asthma limits walking on the flat
9018	663y.00	Number of asthma exacerbations in past year
9552	66Y5.00	Change in asthma management plan
9663	66Y9.00	Step up change in asthma management plan
18223	66YA.00	Step down change in asthma management plan
41020	66YC.00	Absent from work or school due to asthma
10043	66YJ.00	Asthma annual review
13176	66YK.00	Asthma follow-up
102170	66Yp.00	Asthma review using Roy Colleg of Physicians three questions
31167	66YP.00	Asthma night-time symptoms
102400	66Yq.00	Asthma causes night time symptoms 1 to 2 times per week
102395	66Yr.00	Asthma causes symptoms most nights
103612	66Ys.00	Asthma never causes night symptoms
107167	66Yu.00	Number days absent from school due to asthma in past 6 month
24506	8791	Further asthma - drug prevent.
29645	8793	Asthma control step 0
16785	8794	Asthma control step 1
16667	8795	Asthma control step 2
18224	8796	Asthma control step 3
20886	8797	Asthma control step 4
20860	8798	Asthma control step 5
10274	8B3j.00	Asthma medication review
25791	8CR0.00	Asthma clinical management plan
5515	9N1d.00	Seen in asthma clinic
6181	H061400	Obliterating fibrous bronchiolitis
26125	H312300	Bronchiolitis obliterans
70787	H32y100	Atrophic (senile) emphysema
78	H33..00	Asthma
1555	H33..11	Bronchial asthma
7146	H330.00	Extrinsic (atopic) asthma
2290	H330.11	Allergic asthma
1208	H330.12	Childhood asthma
15248	H330.13	Hay fever with asthma
7731	H330.14	Pollen asthma
14777	H330000	Extrinsic asthma without status asthmaticus
5627	H330011	Hay fever with asthma
27926	H330100	Extrinsic asthma with status asthmaticus
6707	H330111	Extrinsic asthma with asthma attack
45782	H330z00	Extrinsic asthma NOS
5267	H331.00	Intrinsic asthma
3665	H331.11	Late onset asthma
29325	H331000	Intrinsic asthma without status asthmaticus
58196	H331100	Intrinsic asthma with status asthmaticus
18323	H331111	Intrinsic asthma with asthma attack

45073	H331z00	Intrinsic asthma NOS
25796	H332.00	Mixed asthma
40823	H334.00	Brittle asthma
4442	H33z.00	Asthma unspecified
32727	H33z.11	Hyperreactive airways disease
4892	H33z000	Status asthmaticus NOS
233	H33z011	Severe asthma attack
232	H33z100	Asthma attack
8335	H33z111	Asthma attack NOS
12987	H33z200	Late-onset asthma
16070	H33zz00	Asthma NOS
4606	H33zz11	Exercise induced asthma
21232	H33zz12	Allergic asthma NEC
18207	H33zz13	Allergic bronchitis NEC
2195	H34..00	Bronchiectasis
20364	H340.00	Recurrent bronchiectasis
41491	H341.00	Post-infective bronchiectasis
32679	H34z.00	Bronchiectasis NOS
93353	H35y600	Sequoiosis (red-cedar asthma)
39478	H35y700	Wood asthma
25013	H4...11	Pneumoconioses
21257	H4...12	Occupational lung disease
19492	H40..00	Coal workers' pneumoconiosis
8303	H41..00	Asbestosis
5005	H410.00	Pleural plaque disease due to asbestosis
100994	H410.11	Asbestos-induced pleural plaque
51410	H41z.00	Asbestosis NOS
46460	H42..00	Silica and silicate pneumoconiosis
60805	H420.00	Talc pneumoconiosis
62233	H421.00	Simple silicosis
71853	H422.00	Complicated silicosis
89206	H423.00	Massive silicotic fibrosis
23446	H42z.00	Silica pneumoconiosis NOS
65376	H43..00	Pneumoconiosis due to other inorganic dust
94894	H431.00	Bauxite fibrosis of lung
49194	H432.00	Berylliosis
94575	H433.00	Graphite fibrosis of lung
30235	H434.00	Siderosis
93577	H435.00	Stannosis
23461	H43z.00	Pneumoconiosis due to inorganic dust NOS
60313	H44..00	Pneumopathy due to inhalation of other dust
37365	H440.00	Byssinosis
26442	H441.00	Cannabinosis
73414	H44z.00	Pneumopathy due to inhalation of other dust NOS
31423	H45..00	Pneumoconiosis NOS
63172	H450.00	Pneumoconiosis associated with tuberculosis

47142	H464.00	Chronic respiratory conditions due to chemical fumes
64721	H464000	Chronic emphysema due to chemical fumes
63216	H464100	Obliterative bronchiolitis due to chemical fumes
47782	H464200	Chronic pulmonary fibrosis due to chemical fumes
70815	H464z00	Chronic respiratory conditions due to chemical fumes NOS
47684	H47y000	Detergent asthma
69914	H4y1.00	Chronic pulmonary radiation disease
22536	H4y1000	Chronic pulmonary fibrosis following radiation
50374	H4y1z00	Chronic pulmonary radiation disease NOS
43417	H4y2100	Chronic drug-induced interstitial lung disorders
61119	H560.00	Pulmonary alveolar proteinosis
27348	H561.00	Idiopathic pulmonary haemosiderosis
68814	H562.00	Pulmonary alveolar microlithiasis
6837	H563.00	Idiopathic fibrosing alveolitis
63174	H563.11	Hamman - Rich syndrome
5519	H563.12	Cryptogenic fibrosing alveolitis
103753	H563.13	Idiopathic pulmonary fibrosis
6051	H563100	Diffuse pulmonary fibrosis
103472	H563200	Pulmonary fibrosis
103559	H563300	Usual interstitial pneumonitis
28229	H563z00	Idiopathic fibrosing alveolitis NOS
22835	H564.00	Bronchiolitis obliterans organising pneumonia
103475	H564.11	Cryptogenic organising pneumonia
61991	H56y000	Endogenous lipoid pneumonia
22905	H581.00	Interstitial emphysema
54893	H582.00	Compensatory emphysema
106650	H583200	Eosinophilic bronchitis
24814	H591.00	Chronic respiratory failure
94486	H593.00	Chronic type 2 respiratory failure
67278	Hyu3.00	[X]Chronic lower respiratory diseases
105939	Hyu4000	[X]Pneumoconiosis due to other dust containing silica
105628	Hyu4800	[X]Chronic+other pulmonary manifestations due to radiation
65060	Hyu5000	[X]Other interstitial pulmonary diseases with fibrosis
9913	1O1..00	Heart failure confirmed
7251	33BA.00	Impaired left ventricular function
11284	585f.00	Echocardiogram shows left ventricular systolic dysfunction
11351	585g.00	Echocardiogram shows left ventricular diastolic dysfunction
18853	662f.00	New York Heart Association classification - class I
13189	662g.00	New York Heart Association classification - class II
19066	662h.00	New York Heart Association classification - class III
51214	662i.00	New York Heart Association classification - class IV
83502	662p.00	Heart failure 6 month review
12366	662T.00	Congestive heart failure monitoring
30779	662W.00	Heart failure annual review
24503	8B29.00	Cardiac failure therapy
32898	8H2S.00	Admit heart failure emergency

17851	8HBE.00	Heart failure follow-up
12627	9N0k.00	Seen in heart failure clinic
19002	9N2p.00	Seen by community heart failure nurse
46294	G41..00	Chronic pulmonary heart disease
54113	G41y.00	Other chronic pulmonary heart disease
71046	G41yz00	Other chronic pulmonary heart disease NOS
15782	G41z.00	Chronic pulmonary heart disease NOS
5695	G41z.11	Chronic cor pulmonale
2062	G58..00	Heart failure
1223	G58..11	Cardiac failure
398	G580.00	Congestive heart failure
2906	G580.11	Congestive cardiac failure
10079	G580.12	Right heart failure
10154	G580.13	Right ventricular failure
9524	G580.14	Biventricular failure
23707	G580000	Acute congestive heart failure
32671	G580100	Chronic congestive heart failure
27884	G580200	Decompensated cardiac failure
11424	G580300	Compensated cardiac failure
94870	G580400	Congestive heart failure due to valvular disease
884	G581.00	Left ventricular failure
23481	G581.11	Asthma - cardiac
43618	G581.12	Pulmonary oedema - acute
5942	G581.13	Impaired left ventricular function
5255	G581000	Acute left ventricular failure
27964	G582.00	Acute heart failure
101138	G583.00	Heart failure with normal ejection fraction
101137	G583.11	HFNEF - heart failure with normal ejection fraction
106897	G583.12	Heart failure with preserved ejection fraction
104275	G584.00	Right ventricular failure
4024	G58z.00	Heart failure NOS
12590	G58z.11	Weak heart
17278	G58z.12	Cardiac failure NOS
8966	G5yy900	Left ventricular systolic dysfunction
12550	G5yyA00	Left ventricular diastolic dysfunction
104876	G5yyB00	Right ventricular diastolic dysfunction
104333	G5yyC00	Diastolic dysfunction
107397	G5yyD00	Left ventricular cardiac dysfunction
24185	R055100	[D]Cardiogenic shock
93947	R055111	[D]Heart shock
20324	R2y1000	[D]Cardiorespiratory failure
6639	14G1.00	H/O: rheumatoid arthritis
4502	43F1.00	Rheumatoid factor positive
29339	66H..00	Rheumatol. disorder monitoring
17412	66H..13	Rheumatoid arthrit. monitoring
15575	66H3.00	Rheumat.dis.- joints affected

29644	66H4.00	Rheumat. symptom change
72098	66H5.00	Rheumat. drug side effect
53649	66H6.00	Rheumat. treatment change
44257	66H6.11	Rheumat.dis.treatment changed
29646	66H7.00	Rheumat.dis.treatment started
36154	66H8.00	Rheumat.dis.treatment stopped
100443	66HB.00	Rheumatology disorder annual review
105507	66HB000	Rheumatoid arthritis annual review
100820	66HC.00	Rheumatic disorder annual review invitation
21911	66HZ.00	Rheumatol.dis. monitoring NOS
3865	AD5..00	Sarcoidosis
33980	AD50.00	Sarcoidosis of lung
49075	AD51.00	Sarcoidosis of lymph nodes
58841	AD52.00	Sarcoidosis of lung with sarcoidosis of lymph nodes
27769	AD53.00	Sarcoidosis of skin
28952	AD53000	Lupus pernio
72595	AD54.00	Sarcoidosis of inferior turbinates
40613	AD55.00	Sarcoid arthropathy
20455	C332100	Cryoglobulinaemic vasculitis
73284	Cyu0600	[X]Sarcoidosis of other and combined sites
49454	F013.00	Meningitis due to sarcoidosis
55612	F326300	Multiple cranial nerve palsies in sarcoidosis
57313	F371.00	Polyneuropathy in collagen vascular disease
44095	F371000	Polyneuropathy in disseminated lupus erythematosus
47465	F371100	Polyneuropathy in polyarteritis nodosa
62401	F371200	Polyneuropathy in rheumatoid arthritis
71258	F371z00	Polyneuropathy in collagen vascular disease NOS
40751	F374900	Polyneuropathy in sarcoidosis
108072	F396100	Myopathy due to disseminated lupus erythematosus
57888	F396300	Myopathy due to polyarteritis nodosa
31209	F396400	Myopathy due to rheumatoid arthritis
52519	F396500	Myopathy due to sarcoidosis
55601	F396600	Myopathy due to scleroderma
21022	F396700	Myopathy due to Sjogren's disease
47037	G558300	Sarcoid heart disease
34437	G5y7.00	Sarcoid myocarditis
49787	G5y8.00	Rheumatoid myocarditis
43816	G5yA.00	Rheumatoid carditis
62323	G75..00	Polyarteritis nodosa and allied conditions
1471	G750.00	Polyarteritis nodosa
98769	G750.11	Necrotising angiitis
102193	G751.00	Acute febrile mucocutaneous lymph node syndrome
6157	G751000	Kawasaki disease
93037	G751z00	Acute febrile mucocutaneous lymph node syndrome NOS
20509	G752.00	Hypersensitivity angiitis
62277	G752.11	Hypersensitivity arteritis

26860	G752000	Goodpasture's syndrome
107564	G752111	Antiglomerular basement membrane disease
107045	G752112	Anti GBM disease - Antiglomerular basement membrane disease
23569	G752z00	Hypersensitivity angiitis NOS
4810	G754.00	Wegener's granulomatosis
109112	G754.11	
10432	G755.00	Giant cell arteritis
9843	G755000	Cranial arteritis
3275	G755100	Temporal arteritis
49149	G755200	Horton's disease
68403	G755z00	Giant cell arteritis NOS
37640	G757.00	Takayasu's disease
19107	G757.11	Aortic arch arteritis
33963	G757.12	Pulseless disease
21602	G758.00	Churg-Strauss vasculitis
18380	G759.00	Juvenile polyarteritis
104312	G75A.00	Microscopic polyangiitis
68136	G75z.00	Polyarteritis nodosa and allied conditions NOS
4649	G766.00	Arteritis unspecified
23533	G766.11	Aortitis
1470	G76B.00	Vasculitis
9954	H570.00	Rheumatoid lung
64799	H571.00	Rheumatic pneumonia
94996	H572.00	Lung disease with systemic sclerosis
42940	H57y100	Lung disease with polymyositis
3859	H57y200	Pulmonary sarcoidosis
47364	H57y300	Lung disease with Sjogren's disease
31564	H57y400	Lung disease with systemic lupus erythematosus
26405	J63A.00	Hepatic granulomas in sarcoidosis
58750	K01x300	Nephrotic syndrome in polyarteritis nodosa
47672	K01x400	Nephrotic syndrome in systemic lupus erythematosus
22205	K01x411	Lupus nephritis
105976	K0H..00	Acute scleroderma renal crisis
107382	K0J0.00	Renal involvement in scleroderma
7871	N000.00	Systemic lupus erythematosus
20007	N000000	Disseminated lupus erythematosus
57675	N000100	Libman-Sacks disease
36942	N000200	Drug-induced systemic lupus erythematosus
29519	N000300	Systemic lupus erythematosus with organ or sys involv
11920	N000400	Systemic lupus erythematosus with pericarditis
99435	N000500	Neonatal lupus erythematosus
101433	N000600	Cerebral lupus
42719	N000z00	Systemic lupus erythematosus NOS
3670	N001.00	Scleroderma
68277	N001.11	Acrosclerosis
28417	N001.12	Systemic sclerosis

44141	N001000	Progressive systemic sclerosis
17675	N001100	CREST syndrome
2360	N002.00	Sicca (Sjogren's) syndrome
1928	N002.11	Keratoconjunctivitis sicca
15511	N004.00	Polymyositis
23834	N005.00	Adult Still's Disease
27603	N04..00	Rheumatoid arthritis and other inflammatory polyarthropathy
844	N040.00	Rheumatoid arthritis
44743	N040000	Rheumatoid arthritis of cervical spine
44203	N040100	Other rheumatoid arthritis of spine
21358	N040200	Rheumatoid arthritis of shoulder
107963	N040300	Rheumatoid arthritis of sternoclavicular joint
100914	N040400	Rheumatoid arthritis of acromioclavicular joint
59738	N040500	Rheumatoid arthritis of elbow
63365	N040600	Rheumatoid arthritis of distal radio-ulnar joint
48832	N040700	Rheumatoid arthritis of wrist
42299	N040800	Rheumatoid arthritis of MCP joint
41941	N040900	Rheumatoid arthritis of PIP joint of finger
63198	N040A00	Rheumatoid arthritis of DIP joint of finger
49067	N040B00	Rheumatoid arthritis of hip
100776	N040C00	Rheumatoid arthritis of sacro-iliac joint
50863	N040D00	Rheumatoid arthritis of knee
107791	N040E00	Rheumatoid arthritis of tibio-fibular joint
51239	N040F00	Rheumatoid arthritis of ankle
73619	N040G00	Rheumatoid arthritis of subtalar joint
70658	N040H00	Rheumatoid arthritis of talonavicular joint
71784	N040J00	Rheumatoid arthritis of other tarsal joint
51238	N040K00	Rheumatoid arthritis of 1st MTP joint
99414	N040L00	Rheumatoid arthritis of lesser MTP joint
107112	N040M00	Rheumatoid arthritis of IP joint of toe
30548	N040N00	Rheumatoid vasculitis
6916	N040P00	Seronegative rheumatoid arthritis
18155	N040Q00	Rheumatoid bursitis
53621	N040R00	Rheumatoid nodule
31054	N040S00	Rheumatoid arthritis - multiple joint
8350	N040T00	Flare of rheumatoid arthritis
23552	N041.00	Felty's syndrome
49227	N042.00	Other rheumatoid arthropathy + visceral/systemic involvement
46436	N042100	Rheumatoid lung disease
5723	N042200	Rheumatoid nodule
37431	N042z00	Rheumatoid arthropathy + visceral/systemic involvement NOS
4186	N043.00	Juvenile rheumatoid arthritis - Still's disease
50644	N043000	Juvenile rheumatoid arthropathy unspecified
47831	N043100	Acute polyarticular juvenile rheumatoid arthritis
21533	N043200	Pauciarticular juvenile rheumatoid arthritis
36276	N043300	Monarticular juvenile rheumatoid arthritis

27557	N043z00	Juvenile rheumatoid arthritis NOS
31360	N045500	Juvenile rheumatoid arthritis
9707	N047.00	Seropositive errosive rheumatoid arthritis
12019	N04X.00	Seropositive rheumatoid arthritis, unspecified
31724	N04y000	Rheumatoid lung
56838	N04y011	Caplan's syndrome
28853	N04y012	Fibrosing alveolitis associated with rheumatoid arthritis
32001	N04y200	Adult-onset Still's disease
1408	N20..00	Polymyalgia rheumatica
3042	N20..11	Polymyalgia
29472	N200.00	Giant cell arteritis with polymyalgia rheumatica
47718	N233200	Myositis in sarcoidosis
106440	Nyu1000	[X]Rheumatoid arthritis+involvement/other organs or systems
93715	Nyu1100	[X]Other seropositive rheumatoid arthritis
70221	Nyu1200	[X]Other specified rheumatoid arthritis
56202	Nyu1G00	[X]Seropositive rheumatoid arthritis, unspecified
52860	Nyu4.00	[X]Systemic connective tissue disorders
53789	Nyu4100	[X]Other giant cell arteritis
58706	Nyu4300	[X]Other forms of systemic lupus erythematosus
71763	Nyu4500	[X]Other forms of systemic sclerosis
67149	Nyu4600	[X]Other overlap syndromes
68965	Nyu4700	[X]Other systemic diseases of connective tissue
92421	Nyu4C00	[X]Systemic disorders/connective tissue in other diseases CE
83529	Nyu4F00	[X]Mixed connective tissue disease
5931	1461	H/O: dementia
55023	66h..00	Dementia monitoring
12710	6AB..00	Dementia annual review
85853	9Ou..00	Dementia monitoring administration
49674	9Ou1.00	Dementia monitoring first letter
83576	9Ou2.00	Dementia monitoring second letter
89036	9Ou3.00	Dementia monitoring third letter
89037	9Ou4.00	Dementia monitoring verbal invite
65235	9Ou5.00	Dementia monitoring telephone invite
38286	A411.00	Jakob-Creutzfeldt disease
1916	E00..11	Senile dementia
1350	E00..12	Senile/presenile dementia
7323	E000.00	Uncomplicated senile dementia
15165	E001.00	Presenile dementia
42602	E001000	Uncomplicated presenile dementia
49513	E001100	Presenile dementia with delirium
30032	E001200	Presenile dementia with paranoia
27677	E001300	Presenile dementia with depression
38438	E001z00	Presenile dementia NOS
44674	E002.00	Senile dementia with depressive or paranoid features
18386	E002000	Senile dementia with paranoia
21887	E002100	Senile dementia with depression

41089	E002z00	Senile dementia with depressive or paranoid features NOS
37015	E003.00	Senile dementia with delirium
19477	E004.00	Arteriosclerotic dementia
8634	E004.11	Multi infarct dementia
43089	E004000	Uncomplicated arteriosclerotic dementia
56912	E004100	Arteriosclerotic dementia with delirium
55467	E004200	Arteriosclerotic dementia with paranoia
43292	E004300	Arteriosclerotic dementia with depression
42279	E004z00	Arteriosclerotic dementia NOS
54505	E012.00	Other alcoholic dementia
27342	E012.11	Alcoholic dementia NOS
62132	E02y100	Drug-induced dementia
25386	E041.00	Dementia in conditions EC
7664	Eu00.00	[X]Dementia in Alzheimer's disease
49263	Eu00000	[X]Dementia in Alzheimer's disease with early onset
25704	Eu00011	[X]Presenile dementia,Alzheimer's type
60059	Eu00012	[X]Primary degen dementia, Alzheimer's type, presenile onset
61528	Eu00013	[X]Alzheimer's disease type 2
38678	Eu00100	[X]Dementia in Alzheimer's disease with late onset
46762	Eu00111	[X]Alzheimer's disease type 1
11379	Eu00112	[X]Senile dementia,Alzheimer's type
43346	Eu00113	[X]Primary degen dementia of Alzheimer's type, senile onset
30706	Eu00200	[X]Dementia in Alzheimer's dis, atypical or mixed type
29386	Eu00z00	[X]Dementia in Alzheimer's disease, unspecified
8195	Eu00z11	[X]Alzheimer's dementia unspec
6578	Eu01.00	[X]Vascular dementia
9565	Eu01.11	[X]Arteriosclerotic dementia
46488	Eu01000	[X]Vascular dementia of acute onset
11175	Eu01100	[X]Multi-infarct dementia
55838	Eu01111	[X]Predominantly cortical dementia
8934	Eu01200	[X]Subcortical vascular dementia
31016	Eu01300	[X]Mixed cortical and subcortical vascular dementia
55313	Eu01y00	[X]Other vascular dementia
19393	Eu01z00	[X]Vascular dementia, unspecified
12621	Eu02.00	[X]Dementia in other diseases classified elsewhere
28402	Eu02000	[X]Dementia in Pick's disease
54106	Eu02100	[X]Dementia in Creutzfeldt-Jakob disease
37014	Eu02200	[X]Dementia in Huntington's disease
9509	Eu02300	[X]Dementia in Parkinson's disease
41185	Eu02400	[X]Dementia in human immunodef virus [HIV] disease
26270	Eu02500	[X]Lewy body dementia
64267	Eu02y00	[X]Dementia in other specified diseases classif elsewhere
4693	Eu02z00	[X] Unspecified dementia
48501	Eu02z11	[X] Presenile dementia NOS
34944	Eu02z13	[X] Primary degenerative dementia NOS
4357	Eu02z14	[X] Senile dementia NOS

27759	Eu02z16	[X] Senile dementia, depressed or paranoid type
53446	Eu04100	[X]Delirium superimposed on dementia
26323	Eu10711	[X]Alcoholic dementia NOS
101999	Eu84311	[X]Dementia infantalis
1917	F110.00	Alzheimer's disease
16797	F110000	Alzheimer's disease with early onset
32057	F110100	Alzheimer's disease with late onset
11136	F111.00	Pick's disease
29512	F112.00	Senile degeneration of brain
7572	F116.00	Lewy body disease
59122	Fyu3000	[X]Other Alzheimer's disease
55222	ZS7C500	Language disorder of dementia
29218	42W2.00	Hb. A1C 7-10% - borderline
13604	42W3.00	Hb. A1C > 10% - bad control
1684	66A4.00	Diabetic on oral treatment
8842	66A5.00	Diabetic on insulin
2378	66AJ.00	Diabetic - poor control
9013	66AJ.11	Unstable diabetes
2478	66AJ100	Brittle diabetes
22023	66AJz00	Diabetic - poor control NOS
28769	66AV.00	Diabetic on insulin and oral treatment
711	C10..00	Diabetes mellitus
38986	C100.00	Diabetes mellitus with no mention of complication
24490	C100000	Diabetes mellitus, juvenile type, no mention of complication
1038	C100011	Insulin dependent diabetes mellitus
14803	C100100	Diabetes mellitus, adult onset, no mention of complication
14889	C100111	Maturity onset diabetes
506	C100112	Non-insulin dependent diabetes mellitus
50972	C100z00	Diabetes mellitus NOS with no mention of complication
1682	C101.00	Diabetes mellitus with ketoacidosis
53200	C101000	Diabetes mellitus, juvenile type, with ketoacidosis
54856	C101100	Diabetes mellitus, adult onset, with ketoacidosis
38617	C101y00	Other specified diabetes mellitus with ketoacidosis
42505	C101z00	Diabetes mellitus NOS with ketoacidosis
21482	C102.00	Diabetes mellitus with hyperosmolar coma
40023	C102000	Diabetes mellitus, juvenile type, with hyperosmolar coma
43139	C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
72345	C102z00	Diabetes mellitus NOS with hyperosmolar coma
15690	C103.00	Diabetes mellitus with ketoacidotic coma
42567	C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma
68843	C103100	Diabetes mellitus, adult onset, with ketoacidotic coma
59288	C103y00	Other specified diabetes mellitus with coma
65062	C103z00	Diabetes mellitus NOS with ketoacidotic coma
1647	C108.00	Insulin dependent diabetes mellitus
18505	C108.11	IDDM-Insulin dependent diabetes mellitus
17858	C108.12	Type 1 diabetes mellitus

24423	C108.13	Type I diabetes mellitus
26855	C108400	Unstable insulin dependent diabetes mellitus
60107	C108411	Unstable type I diabetes mellitus
97474	C108412	Unstable type 1 diabetes mellitus
6791	C108800	Insulin dependent diabetes mellitus - poor control
46850	C108811	Type I diabetes mellitus - poor control
45914	C108812	Type 1 diabetes mellitus - poor control
31310	C108900	Insulin dependent diabetes maturity onset
63017	C108911	Type I diabetes mellitus maturity onset
97446	C108912	Type 1 diabetes mellitus maturity onset
56448	C108A00	Insulin-dependent diabetes without complication
95992	C108A11	Type I diabetes mellitus without complication
44440	C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma
42729	C108E11	Type I diabetes mellitus with hypoglycaemic coma
70766	C108E12	Type 1 diabetes mellitus with hypoglycaemic coma
4513	C109.00	Non-insulin dependent diabetes mellitus
5884	C109.11	NIDDM - Non-insulin dependent diabetes mellitus
17859	C109.12	Type 2 diabetes mellitus
18219	C109.13	Type II diabetes mellitus
8403	C109700	Non-insulin dependent diabetes mellitus - poor control
24458	C109711	Type II diabetes mellitus - poor control
45913	C109712	Type 2 diabetes mellitus - poor control
29979	C109900	Non-insulin-dependent diabetes mellitus without complication
109103	C109911	Type II diabetes mellitus without complication
105784	C109912	Type 2 diabetes mellitus without complication
43785	C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
56268	C109D11	Type II diabetes mellitus with hypoglycaemic coma
61071	C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
18278	C109J00	Insulin treated Type 2 diabetes mellitus
37648	C109J11	Insulin treated non-insulin dependent diabetes mellitus
18264	C109J12	Insulin treated Type II diabetes mellitus
36633	C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
52236	C10A.00	Malnutrition-related diabetes mellitus
66675	C10A000	Malnutrition-related diabetes mellitus with coma
33969	C10A100	Malnutrition-related diabetes mellitus with ketoacidosis
11551	C10B.00	Diabetes mellitus induced by steroids
26108	C10B000	Steroid induced diabetes mellitus without complication
43453	C10C.00	Diabetes mellitus autosomal dominant
46624	C10C.11	Maturity onset diabetes in youth
98392	C10C.12	Maturity onset diabetes in youth type 1
36695	C10D.00	Diabetes mellitus autosomal dominant type 2
59991	C10D.11	Maturity onset diabetes in youth type 2
1549	C10E.00	Type 1 diabetes mellitus
12455	C10E.11	Type I diabetes mellitus
51261	C10E.12	Insulin dependent diabetes mellitus
43921	C10E400	Unstable type 1 diabetes mellitus

49949	C10E411	Unstable type I diabetes mellitus
54600	C10E412	Unstable insulin dependent diabetes mellitus
35288	C10E800	Type 1 diabetes mellitus - poor control
105337	C10E811	Type I diabetes mellitus - poor control
72702	C10E812	Insulin dependent diabetes mellitus - poor control
40682	C10E900	Type 1 diabetes mellitus maturity onset
96235	C10E911	Type I diabetes mellitus maturity onset
97849	C10E912	Insulin dependent diabetes maturity onset
69676	C10EA00	Type 1 diabetes mellitus without complication
62613	C10EA11	Type I diabetes mellitus without complication
99719	C10EA12	Insulin-dependent diabetes without complication
39070	C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma
99716	C10EE12	Insulin dependent diabetes mellitus with hypoglycaemic coma
10692	C10EM00	Type 1 diabetes mellitus with ketoacidosis
62209	C10EM11	Type I diabetes mellitus with ketoacidosis
40837	C10EN00	Type 1 diabetes mellitus with ketoacidotic coma
66145	C10EN11	Type I diabetes mellitus with ketoacidotic coma
95636	C10ER00	Latent autoimmune diabetes mellitus in adult
758	C10F.00	Type 2 diabetes mellitus
22884	C10F.11	Type II diabetes mellitus
25627	C10F700	Type 2 diabetes mellitus - poor control
47315	C10F711	Type II diabetes mellitus - poor control
47954	C10F900	Type 2 diabetes mellitus without complication
53392	C10F911	Type II diabetes mellitus without complication
46917	C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
98723	C10FD11	Type II diabetes mellitus with hypoglycaemic coma
1407	C10FJ00	Insulin treated Type 2 diabetes mellitus
64668	C10FJ11	Insulin treated Type II diabetes mellitus
34450	C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
107701	C10FK11	Hyperosmolar non-ketotic state in type II diabetes mellitus
32627	C10FN00	Type 2 diabetes mellitus with ketoacidosis
106528	C10FN11	Type II diabetes mellitus with ketoacidosis
51756	C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
106061	C10FP11	Type II diabetes mellitus with ketoacidotic coma
95539	C10FS00	Maternally inherited diabetes mellitus
51697	C10G.00	Secondary pancreatic diabetes mellitus
96506	C10G000	Secondary pancreatic diabetes mellitus without complication
61122	C10H.00	Diabetes mellitus induced by non-steroid drugs
67212	C10H000	DM induced by non-steroid drugs without complication
43857	C10M.00	Lipoatrophic diabetes mellitus
22487	C10N.00	Secondary diabetes mellitus
94383	C10N000	Secondary diabetes mellitus without complication
93380	C10N100	Cystic fibrosis related diabetes mellitus
33343	C10y.00	Diabetes mellitus with other specified manifestation
63371	C10y100	Diabetes mellitus, adult, + other specified manifestation
10098	C10yy00	Other specified diabetes mellitus with other spec comps

70821	C10yz00	Diabetes mellitus NOS with other specified manifestation
45491	C10z.00	Diabetes mellitus with unspecified complication
68792	C10z000	Diabetes mellitus, juvenile type, + unspecified complication
63762	C10z100	Diabetes mellitus, adult onset, + unspecified complication
64283	C10zy00	Other specified diabetes mellitus with unspecified comps
64357	C10zz00	Diabetes mellitus NOS with unspecified complication
32193	C11y000	Steroid induced diabetes
14980	C314.00	Renal glycosuria
11848	C314.11	Renal diabetes
52212	Cyu2.00	[X]Diabetes mellitus
41686	Cyu2000	[X]Other specified diabetes mellitus
30477	F420700	High risk proliferative diabetic retinopathy
65463	F420800	High risk non proliferative diabetic retinopathy
50960	L180500	Pre-existing diabetes mellitus, insulin-dependent
50609	L180600	Pre-existing diabetes mellitus, non-insulin-dependent
109133	L180700	Pre-existing malnutrition-related diabetes mellitus
55431	L180X00	Pre-existing diabetes mellitus, unspecified
106927	PKyP.00	Diab insipidus,diab mell,optic atrophy and deafness
106926	PKyP.11	Wolfram syndrome
22967	2BBF.00	Retinal abnormality - diabetes related
47328	2BBk.00	O/E - right eye stable treated prolif diabetic retinopathy
52041	2BBl.00	O/E - left eye stable treated prolif diabetic retinopathy
9835	2BBL.00	O/E - diabetic maculopathy present both eyes
52630	2BBo.00	O/E - sight threatening diabetic retinopathy
11433	2BBP.00	O/E - right eye background diabetic retinopathy
11129	2BBQ.00	O/E - left eye background diabetic retinopathy
101881	2BBr.00	Impaired vision due to diabetic retinopathy
13099	2BBR.00	O/E - right eye preproliferative diabetic retinopathy
13103	2BBS.00	O/E - left eye preproliferative diabetic retinopathy
13097	2BBT.00	O/E - right eye proliferative diabetic retinopathy
13101	2BBV.00	O/E - left eye proliferative diabetic retinopathy
13102	2BBW.00	O/E - right eye diabetic maculopathy
13108	2BBX.00	O/E - left eye diabetic maculopathy
27921	2G51000	Foot abnormality - diabetes related
18056	2G5C.00	Foot abnormality - diabetes related
35316	2G5H.00	O/E - Right diabetic foot - ulcerated
35116	2G5L.00	O/E - Left diabetic foot - ulcerated
62384	2G5V.00	O/E - right chronic diabetic foot ulcer
49640	2G5W.00	O/E - left chronic diabetic foot ulcer
16502	C104.00	Diabetes mellitus with renal manifestation
2475	C104.11	Diabetic nephropathy
93922	C104000	Diabetes mellitus, juvenile type, with renal manifestation
35105	C104100	Diabetes mellitus, adult onset, with renal manifestation
13279	C104y00	Other specified diabetes mellitus with renal complications
35107	C104z00	Diabetes mellitus with nephropathy NOS
33254	C105.00	Diabetes mellitus with ophthalmic manifestation

69748	C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation
41389	C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
47377	C105y00	Other specified diabetes mellitus with ophthalmic complicatn
34283	C105z00	Diabetes mellitus NOS with ophthalmic manifestation
16230	C106.00	Diabetes mellitus with neurological manifestation
59903	C106.11	Diabetic amyotrophy
7795	C106.12	Diabetes mellitus with neuropathy
16491	C106.13	Diabetes mellitus with polyneuropathy
67853	C106000	Diabetes mellitus, juvenile, + neurological manifestation
39317	C106100	Diabetes mellitus, adult onset, + neurological manifestation
61523	C106y00	Other specified diabetes mellitus with neurological comps
22573	C106z00	Diabetes mellitus NOS with neurological manifestation
35399	C107.00	Diabetes mellitus with peripheral circulatory disorder
32403	C107.11	Diabetes mellitus with gangrene
32556	C107.12	Diabetes with gangrene
70448	C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder
63357	C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
33807	C107200	Diabetes mellitus, adult with gangrene
69124	C107300	IDDM with peripheral circulatory disorder
56803	C107400	NIDDM with peripheral circulatory disorder
65025	C107z00	Diabetes mellitus NOS with peripheral circulatory disorder
46963	C108000	Insulin-dependent diabetes mellitus with renal complications
61344	C108011	Type I diabetes mellitus with renal complications
21983	C108012	Type 1 diabetes mellitus with renal complications
49276	C108100	Insulin-dependent diabetes mellitus with ophthalmic comps
102740	C108112	Type 1 diabetes mellitus with ophthalmic complications
52283	C108200	Insulin-dependent diabetes mellitus with neurological comps
49146	C108211	Type I diabetes mellitus with neurological complications
61829	C108212	Type 1 diabetes mellitus with neurological complications
52104	C108300	Insulin dependent diabetes mellitus with multiple complicatn
108007	C108311	Type I diabetes mellitus with multiple complications
44443	C108500	Insulin dependent diabetes mellitus with ulcer
51957	C108511	Type I diabetes mellitus with ulcer
68390	C108512	Type 1 diabetes mellitus with ulcer
60499	C108600	Insulin dependent diabetes mellitus with gangrene
6509	C108700	Insulin dependent diabetes mellitus with retinopathy
38161	C108711	Type I diabetes mellitus with retinopathy
41049	C108712	Type 1 diabetes mellitus with retinopathy
24694	C108B00	Insulin dependent diabetes mellitus with mononeuropathy
99231	C108B11	Type I diabetes mellitus with mononeuropathy
41716	C108C00	Insulin dependent diabetes mellitus with polyneuropathy
57621	C108D00	Insulin dependent diabetes mellitus with nephropathy
66872	C108D11	Type I diabetes mellitus with nephropathy
44260	C108F00	Insulin dependent diabetes mellitus with diabetic cataract
17545	C108F11	Type I diabetes mellitus with diabetic cataract
64446	C108G00	Insulin dependent diab mell with peripheral angiopathy

65616	C108H00	Insulin dependent diabetes mellitus with arthropathy
62352	C108H11	Type I diabetes mellitus with arthropathy
39809	C108J00	Insulin dependent diab mell with neuropathic arthropathy
60208	C108J11	Type I diabetes mellitus with neuropathic arthropathy
18230	C108J12	Type 1 diabetes mellitus with neuropathic arthropathy
46290	C108y00	Other specified diabetes mellitus with multiple comps
64449	C108z00	Unspecified diabetes mellitus with multiple complications
52303	C109000	Non-insulin-dependent diabetes mellitus with renal comps
50225	C109011	Type II diabetes mellitus with renal complications
18209	C109012	Type 2 diabetes mellitus with renal complications
50429	C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
59725	C109111	Type II diabetes mellitus with ophthalmic complications
70316	C109112	Type 2 diabetes mellitus with ophthalmic complications
55842	C109200	Non-insulin-dependent diabetes mellitus with neuro comps
67905	C109211	Type II diabetes mellitus with neurological complications
45919	C109212	Type 2 diabetes mellitus with neurological complications
62146	C109300	Non-insulin-dependent diabetes mellitus with multiple comps
108005	C109312	Type 2 diabetes mellitus with multiple complications
34912	C109400	Non-insulin dependent diabetes mellitus with ulcer
55075	C109411	Type II diabetes mellitus with ulcer
65704	C109412	Type 2 diabetes mellitus with ulcer
40401	C109500	Non-insulin dependent diabetes mellitus with gangrene
62107	C109511	Type II diabetes mellitus with gangrene
46150	C109512	Type 2 diabetes mellitus with gangrene
17262	C109600	Non-insulin-dependent diabetes mellitus with retinopathy
58604	C109611	Type II diabetes mellitus with retinopathy
42762	C109612	Type 2 diabetes mellitus with retinopathy
72320	C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
50813	C109A11	Type II diabetes mellitus with mononeuropathy
45467	C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
47409	C109B11	Type II diabetes mellitus with polyneuropathy
59365	C109C00	Non-insulin dependent diabetes mellitus with nephropathy
64571	C109C11	Type II diabetes mellitus with nephropathy
24836	C109C12	Type 2 diabetes mellitus with nephropathy
69278	C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
48192	C109E11	Type II diabetes mellitus with diabetic cataract
44779	C109E12	Type 2 diabetes mellitus with diabetic cataract
54212	C109F00	Non-insulin-dependent d m with peripheral angiopath
54899	C109F11	Type II diabetes mellitus with peripheral angiopathy
60699	C109F12	Type 2 diabetes mellitus with peripheral angiopathy
24693	C109G00	Non-insulin dependent diabetes mellitus with arthropathy
18143	C109G11	Type II diabetes mellitus with arthropathy
49869	C109G12	Type 2 diabetes mellitus with arthropathy
40962	C109H00	Non-insulin dependent d m with neuropathic arthropathy
47816	C109H11	Type II diabetes mellitus with neuropathic arthropathy
66965	C109H12	Type 2 diabetes mellitus with neuropathic arthropathy

100347	C10A500	Malnutritn-relat diabetes melitus wth periph circul complctn
47582	C10E000	Type 1 diabetes mellitus with renal complications
102946	C10E012	Insulin-dependent diabetes mellitus with renal complications
47649	C10E100	Type 1 diabetes mellitus with ophthalmic complications
99311	C10E111	Type I diabetes mellitus with ophthalmic complications
98071	C10E112	Insulin-dependent diabetes mellitus with ophthalmic comps
42831	C10E200	Type 1 diabetes mellitus with neurological complications
101735	C10E212	Insulin-dependent diabetes mellitus with neurological comps
47650	C10E300	Type 1 diabetes mellitus with multiple complications
91942	C10E311	Type I diabetes mellitus with multiple complications
45276	C10E312	Insulin dependent diabetes mellitus with multiple complicat
18683	C10E500	Type 1 diabetes mellitus with ulcer
93878	C10E511	Type I diabetes mellitus with ulcer
98704	C10E512	Insulin dependent diabetes mellitus with ulcer
69993	C10E600	Type 1 diabetes mellitus with gangrene
102112	C10E611	Type I diabetes mellitus with gangrene
109051	C10E612	Insulin dependent diabetes mellitus with gangrene
18387	C10E700	Type 1 diabetes mellitus with retinopathy
95343	C10E711	Type I diabetes mellitus with retinopathy
93875	C10E712	Insulin dependent diabetes mellitus with retinopathy
68105	C10EB00	Type 1 diabetes mellitus with mononeuropathy
46301	C10EC00	Type 1 diabetes mellitus with polyneuropathy
91943	C10EC11	Type I diabetes mellitus with polyneuropathy
101311	C10EC12	Insulin dependent diabetes mellitus with polyneuropathy
10418	C10ED00	Type 1 diabetes mellitus with nephropathy
102163	C10ED12	Insulin dependent diabetes mellitus with nephropathy
49554	C10EF00	Type 1 diabetes mellitus with diabetic cataract
100770	C10EF12	Insulin dependent diabetes mellitus with diabetic cataract
93468	C10EG00	Type 1 diabetes mellitus with peripheral angiopathy
18642	C10EH00	Type 1 diabetes mellitus with arthropathy
54008	C10EJ00	Type 1 diabetes mellitus with neuropathic arthropathy
30323	C10EK00	Type 1 diabetes mellitus with persistent proteinuria
30294	C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
102620	C10EL11	Type I diabetes mellitus with persistent microalbuminuria
22871	C10EP00	Type 1 diabetes mellitus with exudative maculopathy
97894	C10EP11	Type I diabetes mellitus with exudative maculopathy
55239	C10EQ00	Type 1 diabetes mellitus with gastroparesis
108724	C10EQ11	Type I diabetes mellitus with gastroparesis
18777	C10F000	Type 2 diabetes mellitus with renal complications
57278	C10F011	Type II diabetes mellitus with renal complications
47321	C10F100	Type 2 diabetes mellitus with ophthalmic complications
100964	C10F111	Type II diabetes mellitus with ophthalmic complications
34268	C10F200	Type 2 diabetes mellitus with neurological complications
98616	C10F211	Type II diabetes mellitus with neurological complications
65267	C10F300	Type 2 diabetes mellitus with multiple complications
43227	C10F311	Type II diabetes mellitus with multiple complications

49074	C10F400	Type 2 diabetes mellitus with ulcer
91646	C10F411	Type II diabetes mellitus with ulcer
12736	C10F500	Type 2 diabetes mellitus with gangrene
104323	C10F511	Type II diabetes mellitus with gangrene
18496	C10F600	Type 2 diabetes mellitus with retinopathy
49655	C10F611	Type II diabetes mellitus with retinopathy
62674	C10FA00	Type 2 diabetes mellitus with mononeuropathy
95351	C10FA11	Type II diabetes mellitus with mononeuropathy
18425	C10FB00	Type 2 diabetes mellitus with polyneuropathy
50527	C10FB11	Type II diabetes mellitus with polyneuropathy
12640	C10FC00	Type 2 diabetes mellitus with nephropathy
102201	C10FC11	Type II diabetes mellitus with nephropathy
44982	C10FE00	Type 2 diabetes mellitus with diabetic cataract
93727	C10FE11	Type II diabetes mellitus with diabetic cataract
37806	C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
104639	C10FF11	Type II diabetes mellitus with peripheral angiopathy
59253	C10FG00	Type 2 diabetes mellitus with arthropathy
103902	C10FG11	Type II diabetes mellitus with arthropathy
35385	C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
109197	C10FH11	Type II diabetes mellitus with neuropathic arthropathy
26054	C10FL00	Type 2 diabetes mellitus with persistent proteinuria
60796	C10FL11	Type II diabetes mellitus with persistent proteinuria
18390	C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
85991	C10FM11	Type II diabetes mellitus with persistent microalbuminuria
25591	C10FQ00	Type 2 diabetes mellitus with exudative maculopathy
63690	C10FR00	Type 2 diabetes mellitus with gastroparesis
100292	Cyu2300	[X]Unspecified diabetes mellitus with renal complications
17067	F171100	Autonomic neuropathy due to diabetes
44033	F345000	Diabetic mononeuritis multiplex
17247	F35z000	Diabetic mononeuritis NOS
31790	F372.00	Polyneuropathy in diabetes
5002	F372.11	Diabetic polyneuropathy
2342	F372.12	Diabetic neuropathy
48078	F372000	Acute painful diabetic neuropathy
35785	F372100	Chronic painful diabetic neuropathy
24571	F372200	Asymptomatic diabetic neuropathy
39420	F381300	Myasthenic syndrome due to diabetic amyotrophy
2340	F381311	Diabetic amyotrophy
37315	F3y0.00	Diabetic mononeuropathy
1323	F420.00	Diabetic retinopathy
7069	F420000	Background diabetic retinopathy
3286	F420100	Proliferative diabetic retinopathy
2986	F420200	Preproliferative diabetic retinopathy
10099	F420300	Advanced diabetic maculopathy
3837	F420400	Diabetic maculopathy
47584	F420500	Advanced diabetic retinal disease

10755	F420600	Non proliferative diabetic retinopathy
11626	F420z00	Diabetic retinopathy NOS
17313	F440700	Diabetic iritis
10659	F464000	Diabetic cataract
34152	G73y000	Diabetic peripheral angiopathy
2471	K01x100	Nephrotic syndrome in diabetes mellitus
45499	K01x111	Kimmelstiel - Wilson disease
105302	K08yA00	Proteinuric diabetic nephropathy
107881	K08yA11	Clinical diabetic nephropathy
99628	Kyu0300	[X]Glomerular disorders in diabetes mellitus
7328	M037200	Cellulitis in diabetic foot
24327	M271000	Ischaemic ulcer diabetic foot
11663	M271100	Neuropathic diabetic ulcer - foot
9881	M271200	Mixed diabetic ulcer - foot
18142	N030000	Diabetic cheiroarthropathy
57333	N030011	Diabetic cheiropathy
27891	N030100	Diabetic Charcot arthropathy
53634	R054200	[D]Gangrene of toe in diabetic
31053	R054300	[D]Widespread diabetic foot gangrene
22135	2833	O/E - hemiplegia
36133	2835	O/E - paraplegia
8282	2836	O/E - quadriplegia
1749	F22..00	Hemiplegia
807	F22..11	Hemiparesis
39085	F220.00	Flaccid hemiplegia
20122	F221.00	Spastic hemiplegia
35106	F221.11	Spastic foot
8933	F222.00	Left hemiplegia
8862	F222.11	Left sided weakness
3293	F223.00	Right hemiplegia
2713	F223.11	Right sided weakness
8492	F22z.00	Hemiplegia NOS
99040	F230.11	Paraplegia - congenital
37160	F230000	Congenital paraplegia
27966	F231.00	Congenital hemiplegia
21249	F232.00	Congenital quadriplegia
48126	F232.11	Tetraplegia - congenital
2019	F234.00	Infantile hemiplegia NOS
9271	F240.00	Quadriplegia
16117	F240.11	Tetraplegia
46128	F240000	Flaccid tetraplegia
35540	F240100	Spastic tetraplegia
3063	F241.00	Paraplegia
46175	F241000	Flaccid paraplegia
9375	F241100	Spastic paraplegia
12793	F2A..00	Hemiparesis

65275	F2Az.00	Hemiparesis NOS
104580	F2B0.00	Spastic quadriplegic cerebral palsy
105133	F2B1.00	Spastic hemiplegic cerebral palsy
540	43C3.00	HTLV-3 antibody positive
2835	43C3.11	HIV positive
23770	A788.00	Acquired immune deficiency syndrome
9130	A788.11	Human immunodeficiency virus infection
58857	A788000	Acute human immunodeficiency virus infection
58859	A788100	Asymptomatic human immunodeficiency virus infection
69766	A788200	HIV infection with persistent generalised lymphadenopathy
70869	A788300	Human immunodeficiency virus with constitutional disease
53636	A788400	Human immunodeficiency virus with neurological disease
70528	A788500	Human immunodeficiency virus with secondary infection
101836	A788600	Human immunodeficiency virus with secondary cancers
47632	A788U00	HIV disease result/haematological+immunologic abnorms,NEC
67575	A788W00	HIV disease resulting in unspecified malignant neoplasm
71450	A788X00	HIV disease resulting/unspcf infectious+parasitic disease
62891	A788y00	Human immunodeficiency virus with other clinical findings
36294	A788z00	Acquired human immunodeficiency virus infection syndrome NOS
44303	A789.00	Human immunodef virus resulting in other disease
37006	A789000	HIV disease resulting in mycobacterial infection
66368	A789100	HIV disease resulting in cytomegaloviral disease
23951	A789200	HIV disease resulting in candidiasis
27641	A789300	HIV disease resulting in Pneumocystis carinii pneumonia
104717	A789311	HIV disease resulting in Pneumocystis jirovecii pneumonia
50076	A789400	HIV disease resulting in multiple infections
27853	A789500	HIV disease resulting in Kaposi's sarcoma
108054	A789511	HIV disease resulting in Kaposi sarcoma
44617	A789600	HIV disease resulting in Burkitt's lymphoma
66367	A789700	HIV dis resulting oth types of non-Hodgkin's lymphoma
105324	A789800	HIV disease resulting in multiple malignant neoplasms
65117	A789900	HIV disease resulting in lymphoid interstitial pneumonitis
8281	A789A00	HIV disease resulting in wasting syndrome
51708	A789X00	HIV dis reslt/oth mal neopl/lymph,h'matopoetc+reltd tissu
62854	AyuC.00	[X]Human immunodeficiency virus disease
107807	AyuC100	[X]HIV disease resulting in other viral infections
102117	AyuC300	[X]HIV disease resulting in multiple infections
104134	AyuC400	[X]HIV disease resulting/other infectious+parasitic diseases
69767	AyuC600	[X]HIV disease resulting in other non-Hodgkin's lymphoma
96751	AyuCB00	[X]HIV disease result/haematological+immunologic abnorms,NEC
102252	AyuCC00	[X]HIV disease resulting in other specified conditions
100769	AyuCD00	[X]Unspecified human immunodeficiency virus [HIV] disease
41185	Eu02400	[X]Dementia in human immunodef virus [HIV] disease
104466	L179.00	HIV disease complicating pregnancy childbirth puerperium
44288	R109.00	[D]Laboratory evidence of human immunodeficiency virus [HIV]
24872	ZV01A00	[V]Asymptomatic human immunodeficency virus infection status

101836	A788600	Human immunodeficiency virus with secondary cancers
36147	B153.00	Secondary malignant neoplasm of liver
9618	B56..00	Secondary and unspecified malignant neoplasm of lymph nodes
7830	B56..11	Lymph node metastases
49214	B560.00	Secondary and unspec malig neop lymph nodes head/face/neck
64918	B560000	Secondary and unspec malig neop of superficial parotid LN
66775	B560100	Secondary and unspec malignant neoplasm mastoid lymph nodes
33395	B560200	Secondary and unspec malig neop superficial cervical LN
65253	B560300	Secondary and unspec malignant neoplasm occipital lymph node
92703	B560400	Secondary and unspec malig neop deep parotid lymph nodes
39433	B560500	Secondary and unspec malig neop submandibular lymph nodes
28059	B560600	Secondary and unspec malig neop of facial lymph nodes
38343	B560700	Secondary and unspec malig neop submental lymph nodes
44627	B560800	Secondary and unspec malig neop anterior cervical LN
68611	B560900	Secondary and unspec malig neop deep cervical LN
67129	B560z00	Secondary unspec malig neop lymph nodes head/face/neck NOS
64116	B561.00	Secondary and unspec malig neop intrathoracic lymph nodes
37919	B561000	Secondary and unspec malig neop internal mammary lymph nodes
105953	B561100	Secondary and unspec malig neop intercostal lymph nodes
95378	B561200	Secondary and unspec malig neop diaphragmatic lymph nodes
25366	B561300	Secondary and unspec malig neop ant mediastinal lymph nodes
55463	B561400	Secondary and unspec malig neop post mediastinal lymph nodes
58692	B561500	Secondary and unspec malig neop paratracheal lymph nodes
67797	B561600	Secondary and unspec malig neop superfic tracheobronchial LN
69392	B561700	Secondary and unspec malig neop inferior tracheobronchial LN
62124	B561800	Secondary and unspec malig neop bronchopulmonary lymph nodes
52190	B561900	Secondary and unspec malig neop pulmonary lymph nodes
93716	B561z00	Secondary and unspec malig neop intrathoracic LN NOS
52736	B562.00	Secondary and unspec malig neop intra-abdominal lymph nodes
41691	B562000	Secondary and unspec malig neop coeliac lymph nodes
72713	B562100	Secondary and unspec malig neop superficial mesenteric LN
61677	B562200	Secondary and unspec malig neop inferior mesenteric LN
18658	B562300	Secondary and unspec malig neop common iliac lymph nodes
69132	B562400	Secondary and unspec malig neop external iliac lymph nodes
44931	B562z00	Secondary and unspec malig neop intra-abdominal LN NOS
50199	B563.00	Secondary and unspec malig neop axilla and upper limb LN
37540	B563000	Secondary and unspec malig neop axillary lymph nodes
98626	B563100	Secondary and unspec malig neop supratrochlear lymph nodes
50904	B563200	Secondary and unspec malig neop infraclavicular lymph nodes
46409	B563300	Secondary and unspec malig neop pectoral lymph nodes
73538	B563z00	Secondary and unspec malig neop axilla and upper limb LN NOS
63915	B564.00	Secondary and unspec malig neop inguinal and lower limb LN
54278	B564000	Secondary and unspec malig neop superficial inguinal LN
61289	B564100	Secondary and unspec malig neop deep inguinal lymph nodes
70747	B564z00	Secondary and unspec malig neop of inguinal and leg LN NOS
6701	B565.00	Secondary and unspec malig neop intrapelvic lymph nodes

84368	B565000	Secondary and unspec malig neop internal iliac lymph nodes
101662	B565200	Secondary and unspec malig neop circumflex iliac LN
47366	B565300	Secondary and unspec malig neop sacral lymph nodes
72803	B565z00	Secondary and unspec malig neop intrapelvic LN NOS
20159	B56y.00	Secondary and unspec malig neop lymph nodes multiple sites
15507	B56z.00	Secondary and unspec malig neop lymph nodes NOS
35053	B57..00	Secondary malig neop of respiratory and digestive systems
6471	B57..11	Metastases of respiratory and/or digestive systems
24301	B57..12	Secondary carcinoma of respiratory and/or digestive systems
4137	B570.00	Secondary malignant neoplasm of lung
51551	B571.00	Secondary malignant neoplasm of mediastinum
16213	B572.00	Secondary malignant neoplasm of pleura
62584	B573.00	Secondary malignant neoplasm of other respiratory organs
64680	B574.00	Secondary malignant neoplasm of small intestine and duodenum
55946	B574000	Secondary malignant neoplasm of duodenum
99511	B574200	Secondary malignant neoplasm of ileum
70026	B574z00	Secondary malig neop of small intestine or duodenum NOS
44529	B575.00	Secondary malignant neoplasm of large intestine and rectum
28727	B575000	Secondary malignant neoplasm of colon
62909	B575100	Secondary malignant neoplasm of rectum
36200	B575z00	Secondary malig neop of large intestine or rectum NOS
67396	B576.00	Secondary malig neop of retroperitoneum and peritoneum
35364	B576000	Secondary malignant neoplasm of retroperitoneum
27391	B576100	Secondary malignant neoplasm of peritoneum
8154	B576200	Malignant ascites
97672	B576z00	Secondary malig neop of retroperitoneum or peritoneum NOS
15103	B577.00	Secondary malignant neoplasm of liver
4403	B577.11	Liver metastases
56345	B57y.00	Secondary malignant neoplasm of other digestive organ
66083	B57z.00	Secondary malig neop of respiratory or digestive system NOS
5842	B58..00	Secondary malignant neoplasm of other specified sites
27651	B58..11	Secondary carcinoma of other specified sites
1952	B580.00	Secondary malignant neoplasm of kidney
73213	B581.00	Secondary malignant neoplasm of other urinary organs
60134	B581000	Secondary malignant neoplasm of ureter
22146	B581100	Secondary malignant neoplasm of bladder
53528	B581200	Secondary malignant neoplasm of urethra
62828	B581z00	Secondary malignant neoplasm of other urinary organ NOS
19945	B582.00	Secondary malignant neoplasm of skin
43930	B582000	Secondary malignant neoplasm of skin of head
100296	B582100	Secondary malignant neoplasm of skin of face
35999	B582200	Secondary malignant neoplasm of skin of neck
41144	B582300	Secondary malignant neoplasm of skin of trunk
63896	B582400	Secondary malignant neoplasm of skin of shoulder and arm
48828	B582500	Secondary malignant neoplasm of skin of hip and leg
9505	B582600	Secondary malignant neoplasm of skin of breast

55096	B582z00	Secondary malignant neoplasm of skin NOS
33843	B583.00	Secondary malignant neoplasm of brain and spinal cord
5198	B583000	Secondary malignant neoplasm of brain
38918	B583100	Secondary malignant neoplasm of spinal cord
5199	B583200	Cerebral metastasis
59375	B583z00	Secondary malignant neoplasm of brain or spinal cord NOS
54120	B584.00	Secondary malignant neoplasm of other part of nervous system
7654	B585.00	Secondary malignant neoplasm of bone and bone marrow
18676	B585000	Pathological fracture due to metastatic bone disease
44615	B586.00	Secondary malignant neoplasm of ovary
36401	B587.00	Secondary malignant neoplasm of adrenal gland
18616	B58y.00	Secondary malignant neoplasm of other specified sites
16760	B58y000	Secondary malignant neoplasm of breast
55090	B58y100	Secondary malignant neoplasm of uterus
73616	B58y200	Secondary malignant neoplasm of cervix uteri
97832	B58y211	Secondary cancer of the cervix
70736	B58y300	Secondary malignant neoplasm of vagina
60335	B58y400	Secondary malignant neoplasm of vulva
65490	B58y411	Secondary cancer of the vulva
21590	B58y500	Secondary malignant neoplasm of prostate
34145	B58y600	Secondary malignant neoplasm of testis
49145	B58y700	Secondary malignant neoplasm of penis
104480	B58y800	Secondary malignant neoplasm of epididymis and vas deferens
45824	B58y900	Secondary malignant neoplasm of tongue
22524	B58yz00	Secondary malignant neoplasm of other specified site NOS
16500	B58z.00	Secondary malignant neoplasm of other specified site NOS
54679	B594.00	Secondary malignant neoplasm of unknown site
3197	BB03.00	[M]Neoplasm, metastatic
6985	BB03.11	[M]Secondary neoplasm
3152	BB13.00	[M]Carcinoma, metastatic, NOS
9366	BB13.11	[M]Secondary carcinoma
66163	ByuC200	[X]2ndry+unspcf malignant neoplasm lymph nodes/multi regions
57481	ByuC300	[X]Secondary malignant neoplasm/oth+unspc respiratory organs
88022	ByuC400	[X]Secondary malignant neoplasm/oth+unspcfd digestive organs
97091	ByuC500	[X]2ndry malignant neoplasm/bladder+oth+unsp urinary organs
68332	ByuC600	[X]2ndry malignant neoplasm/oth+unspec parts/nervous system
54253	ByuC700	[X]Secondary malignant neoplasm of other specified sites
99898	9kR..00	Chronic hepatitis annual review - enhanced services admin
26367	A707.00	Chronic viral hepatitis
24813	A707000	Chronic viral hepatitis B with delta-agent
41096	A707100	Chronic viral hepatitis B without delta-agent
30586	A707200	Chronic viral hepatitis C
106642	A707300	Chronic viral hepatitis B
32277	A707X00	Chronic viral hepatitis, unspecified
57995	C310200	Hepatorenal glycogenosis
19512	C310400	Glycogenosis with hepatic cirrhosis

8206	C350012	Pigmentary cirrhosis of liver
102922	C370800	Cystic fibrosis related cirrhosis
6863	J61..00	Cirrhosis and chronic liver disease
4743	J612.00	Alcoholic cirrhosis of liver
68376	J612.11	Florid cirrhosis
100474	J612.12	Laennec's cirrhosis
1754	J614.00	Chronic hepatitis
23578	J614000	Chronic persistent hepatitis
9029	J614100	Chronic active hepatitis
7957	J614111	Autoimmune chronic active hepatitis
1755	J614200	Chronic aggressive hepatitis
53480	J614300	Recurrent hepatitis
66534	J614400	Chronic lobular hepatitis
53877	J614y00	Chronic hepatitis unspecified
15489	J614z00	Chronic hepatitis NOS
16725	J615.00	Cirrhosis - non alcoholic
47257	J615.11	Portal cirrhosis
69204	J615100	Multilobular portal cirrhosis
3450	J615300	Diffuse nodular cirrhosis
44676	J615400	Fatty portal cirrhosis
92909	J615500	Hypertrophic portal cirrhosis
40567	J615600	Capsular portal cirrhosis
27438	J615700	Cardiac portal cirrhosis
108819	J615711	Congestive cirrhosis
96664	J615800	Juvenile portal cirrhosis
58184	J615812	Indian childhood cirrhosis
100253	J615C00	Xanthomatous portal cirrhosis
73482	J615D00	Bacterial portal cirrhosis
48928	J615H00	Infectious cirrhosis NOS
55454	J615y00	Portal cirrhosis unspecified
16455	J615z00	Non-alcoholic cirrhosis NOS
22841	J615z11	Macronodular cirrhosis of liver
18739	J615z12	Cryptogenic cirrhosis of liver
1638	J615z13	Cirrhosis of liver NOS
9494	J616.00	Biliary cirrhosis
5638	J616000	Primary biliary cirrhosis
15424	J616100	Secondary biliary cirrhosis
91591	J616200	Biliary cirrhosis of children
58630	J616z00	Biliary cirrhosis NOS
7602	J617000	Chronic alcoholic hepatitis
17219	J635300	Toxic liver disease with chronic persistent hepatitis
64750	J635400	Toxic liver disease with chronic lobular hepatitis
39351	J635500	Toxic liver disease with chronic active hepatitis
44120	J635600	Toxic liver disease with fibrosis and cirrhosis of liver
6015	Jyu7100	[X]Other and unspecified cirrhosis of liver
4405	7800	Transplantation of liver

32025	7800000	Orthotopic transplantation of liver
71422	7800100	Heterotopic transplantation of liver
89445	7800111	Auxillary liver transplant
100073	7800112	Piggy back liver transplant
69194	7800200	Replacement of previous liver transplant
105506	7800400	Orthotopic transplantation of whole liver
97157	7800500	Orthotopic transplantation of liver NEC
99250	7800y00	Other specified transplantation of liver
27319	7800z00	Transplantation of liver NOS
24989	G850.00	Oesophageal varices with bleeding
30655	G851.00	Oesophageal varices without bleeding
44424	G852.00	Oesophageal varices in diseases EC
96756	G852000	Oesophageal varices with bleeding in diseases EC
73139	G852100	Oesophageal varices without bleeding in diseases EC
26319	G852200	Oesophageal varices in cirrhosis of the liver
8363	G852300	Oesophageal varices in alcoholic cirrhosis of the liver
62582	G852z00	Oesophageal varices in diseases EC NOS
10797	G858.00	Oesophageal varices NOS
23511	J622.00	Hepatic coma
22411	J622.11	Encephalopathy - hepatic
5129	J623.00	Portal hypertension
10636	J624.00	Hepatorenal syndrome
6692	SP08600	Liver transplant failure and rejection
9026	ZV42700	[V]Liver transplanted
20196	14V2.00	H/O: renal dialysis
44422	14V2.11	H/O: kidney dialysis
12720	1Z1..00	Chronic renal impairment
29013	1Z10.00	Chronic kidney disease stage 1
12586	1Z11.00	Chronic kidney disease stage 2
12566	1Z12.00	Chronic kidney disease stage 3
12479	1Z13.00	Chronic kidney disease stage 4
12585	1Z14.00	Chronic kidney disease stage 5
94965	1Z15.00	Chronic kidney disease stage 3A
95179	1Z16.00	Chronic kidney disease stage 3B
94789	1Z17.00	Chronic kidney disease stage 1 with proteinuria
97980	1Z17.11	CKD stage 1 with proteinuria
95572	1Z18.00	Chronic kidney disease stage 1 without proteinuria
95146	1Z19.00	Chronic kidney disease stage 2 with proteinuria
97979	1Z19.11	CKD stage 2 with proteinuria
95121	1Z1A.00	Chronic kidney disease stage 2 without proteinuria
97978	1Z1A.11	CKD stage 2 without proteinuria
94793	1Z1B.00	Chronic kidney disease stage 3 with proteinuria
95145	1Z1B.11	CKD stage 3 with proteinuria
95123	1Z1C.00	Chronic kidney disease stage 3 without proteinuria
95188	1Z1C.11	CKD stage 3 without proteinuria
95408	1Z1D.00	Chronic kidney disease stage 3A with proteinuria

95571	1Z1D.11	CKD stage 3A with proteinuria
95175	1Z1E.00	Chronic kidney disease stage 3A without proteinuria
95176	1Z1E.11	CKD stage 3A without proteinuria
95178	1Z1F.00	Chronic kidney disease stage 3B with proteinuria
95180	1Z1F.11	CKD stage 3B with proteinuria
95177	1Z1G.00	Chronic kidney disease stage 3B without proteinuria
100633	1Z1G.11	CKD stage 3B without proteinuria
95122	1Z1H.00	Chronic kidney disease stage 4 with proteinuria
99312	1Z1H.11	CKD stage 4 with proteinuria
95406	1Z1J.00	Chronic kidney disease stage 4 without proteinuria
97587	1Z1J.11	CKD stage 4 without proteinuria
95508	1Z1K.00	Chronic kidney disease stage 5 with proteinuria
99160	1Z1K.11	CKD stage 5 with proteinuria
95405	1Z1L.00	Chronic kidney disease stage 5 without proteinuria
97683	1Z1L.11	CKD stage 5 without proteinuria
19473	66i..00	Chronic kidney disease monitoring
60302	7A60600	Creation of graft fistula for dialysis
96347	7A61900	Ligation of arteriovenous dialysis fistula
107719	7A61A00	Ligation of arteriovenous dialysis graft
2997	7B00.00	Transplantation of kidney
55151	7B00000	Autotransplant of kidney
11745	7B00100	Transplantation of kidney from live donor
66705	7B00111	Allotransplantation of kidney from live donor
24361	7B00200	Transplantation of kidney from cadaver
98364	7B00211	Allotransplantation of kidney from cadaver
105328	7B00212	Cadaveric renal transplant
89924	7B00300	Allotransplantation of kidney from cadaver, heart-beating
96133	7B00400	Allotransplantation kidney from cadaver, heart non-beating
105787	7B00600	Xenograft renal transplant
70874	7B00y00	Other specified transplantation of kidney
5504	7B00z00	Transplantation of kidney NOS
48121	7B01500	Transplant nephrectomy
72004	7B01511	Excision of rejected transplanted kidney
93366	7B0F.00	Interventions associated with transplantation of kidney
90952	7B0F100	Pre-transplantation of kidney work-up, recipient
96095	7B0F200	Pre-transplantation of kidney work-up, live donor
103429	7B0F300	Post-transplantation of kidney examination, recipient
94964	7B0F400	Post-transplantation of kidney examination, live donor
104050	7B0Fy00	OS interventions associated with transplantation of kidney
104049	7B0Fz00	Interventions associated with transplantation of kidney NOS
31549	7L1A.00	Compensation for renal failure
11773	7L1A.11	Dialysis for renal failure
20073	7L1A000	Renal dialysis
101756	7L1A011	Thomas intravascular shunt for dialysis
2994	7L1A100	Peritoneal dialysis
2996	7L1A200	Haemodialysis NEC

71124	7L1A300	Haemofiltration
88597	7L1A400	Automated peritoneal dialysis
30756	7L1A500	Continuous ambulatory peritoneal dialysis
64828	7L1A600	Peritoneal dialysis NEC
48022	7L1Ay00	Other specified compensation for renal failure
64636	7L1Az00	Compensation for renal failure NOS
56760	7L1B.00	Placement ambulatory apparatus compensation renal failure
36442	7L1B.11	Placement ambulatory dialysis apparatus - compens renal fail
8037	7L1B000	Insertion of ambulatory peritoneal dialysis catheter
23773	7L1B100	Removal of ambulatory peritoneal dialysis catheter
104586	7L1B200	Flushing of peritoneal dialysis catheter
59194	7L1By00	Placement ambulatory apparatus- compensate renal failure OS
83513	7L1C.00	Placement other apparatus for compensation for renal failure
30709	7L1C000	Insertion of temporary peritoneal dialysis catheter
107901	7L1Cy00	Placement other apparatus- compensate for renal failure OS
65089	7L1Cz00	Placement other apparatus- compensate for renal failure NOS
71271	9Ot..00	Chronic kidney disease monitoring administration
30739	9Ot0.00	Chronic kidney disease monitoring first letter
72962	9Ot1.00	Chronic kidney disease monitoring second letter
72964	9Ot2.00	Chronic kidney disease monitoring third letter
88494	9Ot3.00	Chronic kidney disease monitoring verbal invite
69679	9Ot4.00	Chronic kidney disease monitoring telephone invite
89332	9Ot5.00	Predicted stage chronic kidney disease
25394	D215000	Anaemia secondary to chronic renal failure
19454	F374A00	Polyneuropathy in uraemia
40956	G500400	Acute pericarditis - uraemic
105760	G72C.00	Ruptured aneurysm of dialysis vascular access
107188	G72D.00	Aneurysm of dialysis arteriovenous fistula
107220	G72D100	Aneurysm of needle site of dialysis arteriovenous fistula
105742	G72D200	Aneurysm of anastomotic site of dialysis AV fistula
107746	Gy1..00	Stenosis of dialysis vascular access
108699	Gy10.00	Stenosis of dialysis arteriovenous graft
106720	Gy21.00	Thrombosis of dialysis arteriovenous fistula
108116	Gy3..00	Occlusion of dialysis vascular access
109135	Gy30.00	Occlusion of dialysis arteriovenous graft
107082	Gy31.00	Occlusion of dialysis arteriovenous fistula
108213	Gy40.00	Infection of dialysis arteriovenous graft
107260	Gy41.00	Infection of dialysis arteriovenous fistula
108759	Gy5..00	Haemorrhage of dialysis vascular access
106975	Gy51.00	Haemorrhage of dialysis arteriovenous fistula
108423	Gy60.00	Rupture of dialysis arteriovenous graft
7804	K02..00	Chronic glomerulonephritis
10647	K02..11	Nephritis - chronic
11875	K02..12	Nephropathy - chronic
34998	K020.00	Chronic proliferative glomerulonephritis
10809	K021.00	Chronic membranous glomerulonephritis

61494	K022.00	Chronic membranoproliferative glomerulonephritis
65064	K023.00	Chronic rapidly progressive glomerulonephritis
60960	K02y.00	Other chronic glomerulonephritis
97758	K02y000	Chronic glomerulonephritis + diseases EC
4669	K02y200	Chronic focal glomerulonephritis
65400	K02y300	Chronic diffuse glomerulonephritis
63615	K02yz00	Other chronic glomerulonephritis NOS
15097	K02z.00	Chronic glomerulonephritis NOS
512	K05..00	Chronic renal failure
10081	K05..11	Chronic uraemia
53852	K05..12	End stage renal failure
104981	K05..13	Chronic kidney disease
6712	K050.00	End stage renal failure
105392	K051.00	Chronic kidney disease stage 1
105383	K052.00	Chronic kidney disease stage 2
104619	K053.00	Chronic kidney disease stage 3
104963	K054.00	Chronic kidney disease stage 4
105151	K055.00	Chronic kidney disease stage 5
350	K06..00	Renal failure unspecified
4809	K06..11	Uraemia NOS
107771	K06..12	Kidney failure unspecified
11787	K060.00	Renal impairment
6842	K060.11	Impaired renal function
21297	K0A3.00	Chronic nephritic syndrome
66505	K0A3000	Chronic nephritic syndrome, minor glomerular abnormality
40413	K0A3100	Chronic nephritic syndrm focal+segmental glomerular lesions
57168	K0A3200	Chron nephritic syndrom difuse membranous glomerulonephritis
56893	K0A3300	Chron neph syn difus mesangial prolifrtiv glomerulonephritis
73026	K0A3500	Chronic neph syn difus mesangiocapillary glomerulonephritis
60198	K0A3600	Chronic nephritic syndrome, dense deposit disease
60857	K0A3700	Chronic nephritic syn diffuse crescentic glomerulonephritis
48057	K0B5.00	Renal tubulo-interstitial disordrs in transplant rejectn
8330	K0D..00	End-stage renal disease
100205	K0E..00	Acute-on-chronic renal failure
106060	K105.00	Chronic infective interstitial nephritis
105746	K13C000	Chronic cyclosporin A nephrotoxicity
101453	Kyu1000	[X]Other chronic tubulo-interstitial nephritis
100693	Kyu1C00	[X]Renal tubulo-interstitial disorders/transplant rejection
61930	Kyu2.00	[X]Renal failure
53940	Kyu2100	[X]Other chronic renal failure
48639	SP01500	Mechanical complication of dialysis catheter
46438	SP05613	[X] Peritoneal dialysis associated peritonitis
101124	SP06B00	Continuous ambulatory peritoneal dialysis associated perit
59315	SP07G00	Stenosis of arteriovenous dialysis fistula
70712	SP08011	Det.ren.func.after ren.transpl
11553	SP08300	Kidney transplant failure and rejection

104905	SP08D00	Acute-on-chronic rejection of renal transplant
104960	SP08E00	Acute rejection of renal transplant - grade I
107000	SP08F00	Acute rejection of renal transplant - grade II
104630	SP08G00	Acute rejection of renal transplant - grade III
104201	SP08H00	Acute rejection of renal transplant
106620	SP08J00	Chronic rejection of renal transplant
105724	SP08N00	Unexplained episode of renal transplant dysfunction
106301	SP08P00	Stenosis of vein of transplanted kidney
105811	SP08R00	Renal transplant rejection
107752	SP08T00	Urological complication of renal transplant
108437	SP08V00	Very mild acute rejection of renal transplant
108705	SP08V11	Borderline changes of acute rejection
106866	SP08W00	Vascular complication of renal transplant
107900	SP0E.00	Disorders associated with peritoneal dialysis
108785	SP0F.00	Haemodialysis first use syndrome
105436	SP0G.00	Anaphylactoid reaction due to haemodialysis
96184	TA02000	Accid cut,puncture,perf,h'ge - kidney dialysis
69266	TA22000	Failure of sterile precautions during kidney dialysis
54990	TB00100	Kidney transplant with complication, without blame
18774	TB00111	Renal transplant with complication, without blame
28158	TB11.00	Kidney dialysis with complication, without blame
66714	TB11.11	Renal dialysis with complication, without blame
5911	ZV42000	[V]Kidney transplanted
22252	ZV45100	[V]Renal dialysis status
60743	ZV56.00	[V]Aftercare involving intermittent dialysis
99692	ZV56000	[V]Aftercare involving extracorporeal dialysis
46145	ZV56011	[V]Aftercare involving renal dialysis NOS
52088	ZV56100	[V]Preparatory care for dialysis
63488	ZV56y00	[V]Other specified aftercare involving intermittent dialysis
45160	ZV56y11	[V]Aftercare involving peritoneal dialysis
63038	ZV56z00	[V]Unspecified aftercare involving intermittent dialysis
35674	14A3.00	H/O: myocardial infarct <60
40399	14A4.00	H/O: myocardial infarct >60
50372	14AH.00	H/O: Myocardial infarction in last year
100139	14AT.00	History of myocardial infarction
241	G30..00	Acute myocardial infarction
13566	G30..11	Attack - heart
2491	G30..12	Coronary thrombosis
30421	G30..13	Cardiac rupture following myocardial infarction (MI)
1204	G30..14	Heart attack
1677	G30..15	MI - acute myocardial infarction
13571	G30..16	Thrombosis - coronary
17689	G30..17	Silent myocardial infarction
12139	G300.00	Acute anterolateral infarction
5387	G301.00	Other specified anterior myocardial infarction
40429	G301000	Acute anteroapical infarction

17872	G301100	Acute anteroseptal infarction
14897	G301z00	Anterior myocardial infarction NOS
8935	G302.00	Acute inferolateral infarction
29643	G303.00	Acute inferoposterior infarction
23892	G304.00	Posterior myocardial infarction NOS
14898	G305.00	Lateral myocardial infarction NOS
63467	G306.00	True posterior myocardial infarction
3704	G307.00	Acute subendocardial infarction
9507	G307000	Acute non-Q wave infarction
10562	G307100	Acute non-ST segment elevation myocardial infarction
1678	G308.00	Inferior myocardial infarction NOS
30330	G309.00	Acute Q-wave infarct
32854	G30B.00	Acute posterolateral myocardial infarction
29758	G30X.00	Acute transmural myocardial infarction of unspecif site
12229	G30X000	Acute ST segment elevation myocardial infarction
34803	G30y.00	Other acute myocardial infarction
28736	G30y000	Acute atrial infarction
62626	G30y100	Acute papillary muscle infarction
41221	G30y200	Acute septal infarction
46017	G30yz00	Other acute myocardial infarction NOS
14658	G30z.00	Acute myocardial infarction NOS
23579	G310.00	Postmyocardial infarction syndrome
15661	G310.11	Dressler's syndrome
68357	G31y100	Microinfarction of heart
4017	G32..00	Old myocardial infarction
16408	G32..11	Healed myocardial infarction
17464	G32..12	Personal history of myocardial infarction
18842	G35..00	Subsequent myocardial infarction
45809	G350.00	Subsequent myocardial infarction of anterior wall
38609	G351.00	Subsequent myocardial infarction of inferior wall
72562	G353.00	Subsequent myocardial infarction of other sites
46166	G35X.00	Subsequent myocardial infarction of unspecified site
36423	G36..00	Certain current complication follow acute myocardial infarct
24126	G360.00	Haemopericardium/current comp folow acut myocard infarct
23708	G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
37657	G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn
59189	G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
59940	G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
69474	G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
29553	G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
32272	G38..00	Postoperative myocardial infarction
46112	G380.00	Postoperative transmural myocardial infarction anterior wall
46276	G381.00	Postoperative transmural myocardial infarction inferior wall
106812	G383.00	Postoperative transmural myocardial infarction unspec site
41835	G384.00	Postoperative subendocardial myocardial infarction
68748	G38z.00	Postoperative myocardial infarction, unspecified

35119	G501.00	Post infarction pericarditis
96838	Gyu3400	[X]Acute transmural myocardial infarction of unspecif site
109035	Gyu3500	[X]Subsequent myocardial infarction of other sites
99991	Gyu3600	[X]Subsequent myocardial infarction of unspecified site
2489	J102.00	Ulcer of oesophagus
24021	J102000	Peptic ulcer of oesophagus
49926	J102100	Fungal ulcer of oesophagus
51013	J102200	Oesophageal ulcer due to aspirin
94752	J102300	Oesophageal ulcer due to chemicals
58603	J102400	Oesophageal ulcer due to medicines
5596	J102500	Barrett's ulcer of oesophagus
42150	J102z00	Ulcer of oesophagus NOS
1262	J11..00	Gastric ulcer - (GU)
6333	J11..11	Prepyloric ulcer
3101	J11..12	Pyloric ulcer
24040	J110.00	Acute gastric ulcer
64165	J110000	Acute gastric ulcer without mention of complication
30054	J110100	Acute gastric ulcer with haemorrhage
11124	J110111	Bleeding acute gastric ulcer
14671	J110200	Acute gastric ulcer with perforation
71403	J110300	Acute gastric ulcer with haemorrhage and perforation
24342	J110y00	Acute gastric ulcer unspecified
44324	J110z00	Acute gastric ulcer NOS
18654	J111.00	Chronic gastric ulcer
48946	J111000	Chronic gastric ulcer without mention of complication
63582	J111100	Chronic gastric ulcer with haemorrhage
36583	J111111	Bleeding chronic gastric ulcer
53336	J111200	Chronic gastric ulcer with perforation
11104	J111211	Perforated chronic gastric ulcer
71897	J111300	Chronic gastric ulcer with haemorrhage and perforation
67356	J111400	Chronic gastric ulcer with obstruction
64556	J111y00	Chronic gastric ulcer unspecified
44309	J111z00	Chronic gastric ulcer NOS
63001	J112.00	Anti-platelet induced gastric ulcer
89227	J112z00	Anti-platelet induced gastric ulcer NOS
89023	J113.00	Non steroidal anti inflammatory drug induced gastric ulcer
97993	J113z00	Non steroidal anti inflammatory drug induced gastric ulc NOS
53081	J11y.00	Unspecified gastric ulcer
73338	J11y000	Unspecified gastric ulcer without mention of complication
57958	J11y100	Unspecified gastric ulcer with haemorrhage
36461	J11y200	Unspecified gastric ulcer with perforation
73697	J11y400	Unspecified gastric ulcer with obstruction
94397	J11yy00	Unspec gastric ulcer; unspec haemorrhage and/or perforation
44284	J11yz00	Unspecified gastric ulcer NOS
29771	J11z.00	Gastric ulcer NOS
2877	J11z.11	Gastric erosions

52323	J11z.12	Multiple gastric ulcers
352	J12..00	Duodenal ulcer - (DU)
18027	J120.00	Acute duodenal ulcer
44335	J120000	Acute duodenal ulcer without mention of complication
18001	J120100	Acute duodenal ulcer with haemorrhage
18324	J120200	Acute duodenal ulcer with perforation
48730	J120300	Acute duodenal ulcer with haemorrhage and perforation
73417	J120400	Acute duodenal ulcer with obstruction
53822	J120y00	Acute duodenal ulcer unspecified
53797	J120z00	Acute duodenal ulcer NOS
9853	J121.00	Chronic duodenal ulcer
33438	J121000	Chronic duodenal ulcer without mention of complication
48951	J121100	Chronic duodenal ulcer with haemorrhage
18625	J121111	Bleeding chronic duodenal ulcer
37643	J121200	Chronic duodenal ulcer with perforation
23087	J121211	Perforated chronic duodenal ulcer
71881	J121300	Chronic duodenal ulcer with haemorrhage and perforation
44073	J121400	Chronic duodenal ulcer with obstruction
52138	J121y00	Chronic duodenal ulcer unspecified
51406	J121z00	Chronic duodenal ulcer NOS
22918	J122.00	Duodenal ulcer disease
3462	J123.00	Duodenal erosion
29317	J124.00	Recurrent duodenal ulcer
89234	J125.00	Anti-platelet induced duodenal ulcer
85989	J126.00	Non steroidal anti inflammatory drug induced duodenal ulcer
53669	J12y.00	Unspecified duodenal ulcer
71150	J12y000	Unspecified duodenal ulcer without mention of complication
2814	J12y100	Unspecified duodenal ulcer with haemorrhage
657	J12y200	Unspecified duodenal ulcer with perforation
93436	J12y300	Unspecified duodenal ulcer with haemorrhage and perforation
71904	J12y400	Unspecified duodenal ulcer with obstruction
28366	J12yy00	Unspec duodenal ulcer; unspec haemorrhage and/or perforation
65737	J12yz00	Unspecified duodenal ulcer NOS
15175	J12z.00	Duodenal ulcer NOS
670	J13..00	Peptic ulcer - (PU) site unspecified
15821	J13..11	Stress ulcer NOS
32856	J130.00	Acute peptic ulcer
68661	J130000	Acute peptic ulcer without mention of complication
44637	J130100	Acute peptic ulcer with haemorrhage
5521	J130200	Acute peptic ulcer with perforation
45304	J130300	Acute peptic ulcer with haemorrhage and perforation
67711	J130y00	Acute peptic ulcer unspecified
50048	J130z00	Acute peptic ulcer NOS
40997	J131.00	Chronic peptic ulcer
99430	J131000	Chronic peptic ulcer without mention of complication
53126	J131100	Chronic peptic ulcer with haemorrhage

37620	J131200	Chronic peptic ulcer with perforation
52313	J131400	Chronic peptic ulcer with obstruction
70390	J131y00	Chronic peptic ulcer unspecified
69663	J131z00	Chronic peptic ulcer NOS
50497	J13y.00	Unspecified peptic ulcer
67082	J13y000	Unspecified peptic ulcer without mention of complication
70456	J13y100	Unspecified peptic ulcer with haemorrhage
64111	J13y200	Unspecified peptic ulcer with perforation
96622	J13y300	Unspecified peptic ulcer with haemorrhage and perforation
99670	J13y400	Unspecified peptic ulcer with obstruction
60249	J13yz00	Unspecified peptic ulcer NOS
19928	J13z.00	Peptic ulcer NOS
16993	14AE.00	H/O: aortic aneurysm
59534	14NB.00	H/O: Peripheral vascular disease procedure
7975	16I..00	Claudication distance
11680	2I16.00	O/E - gangrene
18499	662U.00	Peripheral vascular disease monitoring
103613	66f3.00	Aortic aneurysm monitoring
52358	7A11.00	Replacement of aneurysmal bifurcation of aorta
96654	7A11000	Emerg repl aneurysm bifurc aorta by anast aorta to fem art
56495	7A11100	Replace aneurysm bifurc aorta by anast aorta to femoral art
69922	7A11200	Emerg repl aneurysm bifurc aorta by anast aorta to iliac a
92925	7A11211	Y graft of abdominal Aortic aneurysm (emergency)
56510	7A11300	Replace aneurysm bifurc aorta by anast aorta to iliac artery
51166	7A11311	Y graft abdominal Aortic aneurysm
62301	7A11y00	Replacement of aneurysmal bifurcation of aorta OS
66761	7A11z00	Replacement of aneurysmal bifurcation of aorta NOS
31613	7A13.00	Emergency replacement of aneurysmal segment of aorta
17220	7A13.11	Emergency repair of aortic aneurysm
99722	7A13000	Emerg replace aneurysm asc aorta by anastom aorta to aorta
93060	7A13100	Emerg replace aneurysm thor aorta by anastom aorta to aorta
66232	7A13300	Emerg replace aneurysm infrarenal aorta by anast aorta/aorta
54192	7A13400	Emerg replace aneurysm abdom aorta by anast aorta/aorta NEC
63408	7A13411	Tube graft abdominal Aortic aneurysm (emergency)
45477	7A13y00	Emergency replacement of aneurysmal segment of aorta OS
45474	7A13z00	Emergency replacement of aneurysmal segment of aorta NOS
43108	7A14.00	Other replacement of aneurysmal segment of aorta
1736	7A14.11	Aortic aneurysm repair
64961	7A14000	Replace aneurysm ascend aorta by anast of aorta/aorta NEC
42444	7A14100	Replace aneurysm thoracic aorta by anast of aorta/aorta NEC
54379	7A14200	Replace aneurys suprarenal aorta by anast aorta to aorta NEC
44553	7A14300	Replace aneurys infrarenal aorta by anast aorta to aorta NEC
19996	7A14400	Replace aneurysm abdominal aorta by anast aorta to aorta NEC
26232	7A14411	Tube graft of Abdominal aortic aneurysm
55445	7A14y00	Other replacement of aneurysmal segment of aorta OS
36651	7A14z00	Other replacement of aneurysmal segment of aorta NOS

33430	7A19400	Operation on aneurysm of aorta NEC
93959	7A1B.00	Transluminal operations on aneurysmal segment of aorta
70446	7A1B000	Endovascular stenting infrarenal abdominal aortic aneurysm
97030	7A1B100	Endovascular stenting of suprarenal aortic aneurysm
51061	7A1B200	Endovascular stenting of thoracic aortic aneurysm
95976	7A1B500	Endovascular stenting of aorto-uniiliac aneurysm
100195	7A1B600	Endovascular stenting for aortic aneurysm of bifurcation NEC
97109	7A1B700	Endovascular stenting for aorto-uniiliac aneurysm
97217	7A1B800	Endovascul insert stent infrarenal abdominal aortic aneurysm
106780	7A1B900	Endovascular insertion stent for suprarenal aortic aneurysm
98542	7A1BA00	Endovascular insertion of stent for thoracic aortic aneurysm
99859	7A1BC00	Endovas insert stent for aortic aneurysm of bifurcation NEC
98175	7A1BD00	Endovascular insertion of stent for aorto-uniiliac aneurysm
90861	7A1Bz00	Transluminal operations on aneurysmal segment of aorta NOS
94331	7A1C.00	Translum insert stent graft for aneurysmal segment of aorta
83577	7A1C000	Endovas ins stent graft for infrarenal abdom aortic aneurysm
94682	7A1C100	Endovas insert of stent graft for suprarenal aortic aneurysm
91462	7A1C200	Endov insertion of stent graft for thoracic aortic aneurysm
103427	7A1C500	Endovas insertion of stent graft for aorto-uniiliac aneurysm
98565	7A1Cy00	OS translum ins stent graft for aneurysmal segment of aorta
93627	7A1Cz00	Translum ins stent graft for aneurysmal segment of aorta NOS
21927	7A41.00	Other bypass of iliac artery
101910	7A41.11	Other bypass of iliac artery by anastomosis
44250	7A41000	Emerg bypass iliac art by iliac/femoral art anastomosis NEC
28616	7A41100	Bypass iliac artery by iliac/femoral artery anastomosis NEC
72448	7A41200	Emerg bypass iliac artery by femoral/femoral art anast NEC
43648	7A41211	Emergency femoro-femoral prosthetic cross over graft
36443	7A41300	Bypass iliac artery by femoral/femoral art anastomosis NEC
30989	7A41311	Femoro-femoral prosthetic cross over graft
68141	7A41400	Emerg bypass comm iliac art by aorta/com iliac art anast NEC
66917	7A41600	Emerg bypass leg artery by aorta/com fem art anastomosis NEC
32492	7A41900	Bypass common iliac artery by aorta/com iliac art anast NEC
55554	7A41B00	Bypass leg artery by aorta/com femoral art anastomosis NEC
66804	7A41C00	Bypass leg artery by aorta/deep femoral art anastomosis NEC
100036	7A41D00	Bypass iliac artery by iliac/iliac artery anastomosis NEC
41768	7A41F00	Ilio-femoral prosthetic cross over graft
52357	7A41y00	Other specified other bypass of iliac artery
38921	7A41z00	Other bypass of iliac artery NOS
9099	7A47.00	Other emergency bypass of femoral artery or popliteal artery
72491	7A47.11	Other emerg bypass femoral or popliteal art by anastomosis
100113	7A47.12	Other emergency bypass of common femoral artery
63238	7A47.13	Other emergency bypass of deep femoral artery
39776	7A47.14	Other emergency bypass of popliteal artery
97606	7A47.15	Other emergency bypass of superficial femoral artery
11766	7A47.16	Other emergency bypass of femoral artery
43651	7A47000	Emerg bypass femoral art by fem/pop art anast c prosth NEC

67818	7A47100	Emerg bypass popliteal art by pop/pop art anast c prosth NEC
52342	7A47200	Emerg bypass femoral art by fem/pop a anast c vein graft NEC
60693	7A47300	Emerg bypass pop art by pop/pop art anast c vein graft NEC
66820	7A47400	Emerg bypass femoral art by fem/tib art anast c prosth NEC
96255	7A47600	Emerg bypass femoral art by fem/tib a anast c vein graft NEC
66879	7A47700	Emerg bypass pop art by pop/tib art anast c vein graft NEC
99676	7A47800	Emerg bypass femoral art by fem/peron art anast c prosth NEC
62775	7A47B00	Emerg bypass pop art by pop/peron art anast c vein graft NEC
48939	7A47C00	Emerg bypass femoral artery by fem/fem art anastomosis NEC
70922	7A47D00	Emerg bypass popliteal artery by pop/fem art anastomosis NEC
65692	7A47y00	Other emergency bypass of femoral or popliteal artery OS
68320	7A47z00	Other emergency bypass of femoral or popliteal artery NOS
24692	7A48.00	Other bypass of femoral artery or popliteal artery
61974	7A48.11	Other bypass of femoral or popliteal artery by anastomosis
37787	7A48.12	Other bypass of common femoral artery
18060	7A48.14	Other bypass of femoral artery
12331	7A48.15	Other bypass of popliteal artery
40732	7A48.16	Other bypass of superficial femoral artery
27580	7A48000	Bypass femoral artery by fem/pop art anast c prosthesis NEC
64555	7A48100	Bypass popliteal artery by pop/pop a anast c prosthesis NEC
28030	7A48200	Bypass femoral artery by fem/pop art anast c vein graft NEC
24097	7A48300	Bypass popliteal artery by pop/pop a anast c vein graft NEC
39877	7A48400	Bypass femoral artery by fem/tib art anast c prosthesis NEC
60465	7A48500	Bypass popliteal artery by pop/tib a anast c prosthesis NEC
41823	7A48600	Bypass femoral artery by fem/tib art anast c vein graft NEC
48700	7A48700	Bypass popliteal artery by pop/tib a anast c vein graft NEC
67982	7A48800	Bypass femoral artery by fem/peron a anast c prosthesis NEC
107158	7A48900	Bypass popliteal artery by pop/peron art anast c prosth NEC
53675	7A48A00	Bypass femoral artery by fem/peron a anast c vein graft NEC
68412	7A48B00	Bypass popliteal art by pop/peron art anast c vein graft NEC
45428	7A48C00	Bypass femoral artery by femoral/femoral art anastomosis NEC
42115	7A48D00	Bypass popliteal artery by pop/fem artery anastomosis NEC
22016	7A48E00	Femoro-femoral prosthetic cross over graft
42640	7A48y00	Other bypass of femoral artery or popliteal artery OS
2066	7A48z00	Other bypass of femoral artery or popliteal artery NOS
106224	9m1..00	Peripheral vascular disease monitoring invitation
106260	9m10.00	Peripheral vascular disease monitoring first letter
106660	9m11.00	Peripheral vascular disease monitoring second letter
106855	9m12.00	Peripheral vascular disease monitoring third letter
51204	A3A0.00	Gas gangrene
99592	A3A0000	Gas gangrene caused by clostridium histolyticum
105609	A3A0100	Gas gangrene caused by clostridium oedematiens
99978	A3A0200	Gas gangrene caused by clostridium perfringens
27349	A3A0500	Gas gangrene
105581	A3A0B00	Gas gangrene-hand
99616	A3A0E00	Gas gangrene-leg

72632	A3A0F00	Gas gangrene-foot
1735	G71..00	Aortic aneurysm
16521	G710.00	Dissecting aortic aneurysm
27563	G711.00	Thoracic aortic aneurysm which has ruptured
16800	G711.11	Ruptured thoracic aortic aneurysm
23532	G712.00	Thoracic aortic aneurysm without mention of rupture
17767	G713.00	Abdominal aortic aneurysm which has ruptured
13572	G713.11	Ruptured abdominal aortic aneurysm
63920	G713000	Ruptured suprarenal aortic aneurysm
1867	G714.00	Abdominal aortic aneurysm without mention of rupture
17345	G714.11	AAA - Abdominal aortic aneurysm without mention of rupture
45521	G714000	Juxtarenal aortic aneurysm
28109	G714100	Inflammatory abdominal aortic aneurysm
101379	G714200	Infrarenal abdominal aortic aneurysm
101195	G714300	Aneurysm of suprarenal aorta
15304	G715.00	Ruptured aortic aneurysm NOS
11430	G715000	Thoracoabdominal aortic aneurysm, ruptured
16034	G716.00	Aortic aneurysm without mention of rupture NOS
40787	G716000	Thoracoabdominal aortic aneurysm, without mention of rupture
70260	G717.00	Aortic aneurysm - syphilitic
9759	G718.00	Leaking abdominal aortic aneurysm
6872	G71z.00	Aortic aneurysm NOS
5943	G73..00	Other peripheral vascular disease
5702	G73..11	Peripheral ischaemic vascular disease
1826	G73..12	Ischaemia of legs
6827	G73..13	Peripheral ischaemia
9204	G732.00	Peripheral gangrene
5414	G732000	Gangrene of toe
12735	G732100	Gangrene of foot
39949	G732200	Gangrene of finger
51057	G732300	Gangrene of thumb
23672	G732400	Gangrene of hand
98174	G733.00	Ischaemic foot
105317	G734.00	Peripheral arterial disease
38907	G73y.00	Other specified peripheral vascular disease
23871	G73y100	Peripheral angiopathic disease EC NOS
4325	G73yz00	Other specified peripheral vascular disease NOS
3530	G73z.00	Peripheral vascular disease NOS
1517	G73z000	Intermittent claudication
6853	G73z011	Claudication
101866	G73z012	Vascular claudication
2760	G73zz00	Peripheral vascular disease NOS
18423	G76A.00	Arterial insufficiency
102725	Gyu7100	[X]Aortic aneurysm of unspecified site, ruptured
102719	Gyu7200	[X]Aortic aneurysm of unspecified site, nonruptured
73961	Gyu7400	[X]Other specified peripheral vascular diseases

105621	Gyu7800	[X]Aneurysm of aorta in diseases classified elsewhere
4970	R054.00	[D]Gangrene
51634	R054000	[D]Gangrene, spreading cutaneous
53634	R054200	[D]Gangrene of toe in diabetic
31053	R054300	[D]Widespread diabetic foot gangrene
37750	R054z00	[D]Gangrene NOS

Codes for other comorbidities and demographics

medcode	read_code	description
me_105800	re_22K..00	Baseline body mass index
me_107231	re_22K1.00	Target body mass index
me_108478	re_22K2.00	Obese class III (BMI equal to
me_108610	re_22K3.00	Obese class II (body mass inde
me_108694	re_22K4.00	Obese class I (body mass index
me_13278	re_22K5.00	Body mass index 30+ - obesity
me_22556	re_22K6.00	Body mass index 40+ - severely
me_24496	re_22K7.00	Body mass index less than 20
me_28937	re_22K8.00	Body Mass Index high K/M2
me_28946	re_22KA.00	Body Mass Index normal K/M2
me_32914	re_22KB.00	Body Mass Index low K/M2
me_44291	re_22KC.00	Body mass index 20-24 - normal
me_8105	re_22KD.00	Body Mass Index
me_9015	re_22KE.00	Body mass index index 25-29 -
Smoking Status		
me_12953	re_9OO1.00	ATTENDS STOP SMOKING MONITOR.
me_98137	re_67H6.00	BRIEF INTERVENTION FOR SMOKING CESSATION
me_12963	re_137Y.00	CIGAR CONSUMPTION
me_12943	re_137J.00	CIGAR SMOKER
me_12965	re_137X.00	CIGARETTE CONSUMPTION
me_46300	re_137g.00	CIGARETTE PACK-YEARS
me_93	re_137P.00	CIGARETTE SMOKER
me_60	re_137L.00	CURRENT NON-SMOKER
me_10558	re_137R.00	CURRENT SMOKER
me_12878	re_137T.00	DATE CEASED SMOKING
me_11527	re_9N4M.00	DNA - DID NOT ATTEND SMOKING CESSATION CLINIC
me_19488	re_137O.00	EX CIGAR SMOKER
me_26470	re_137N.00	EX PIPE SMOKER
me_100495	re_137l.00	EX ROLL-UP CIGARETTE SMOKER
me_90	re_137S.00	EX SMOKER
me_97210	re_137j.00	EX-CIGARETTE SMOKER
me_12956	re_137A.00	EX-HEAVY SMOKER (20-39/DAY)
me_12957	re_1378.00	EX-LIGHT SMOKER (1-9/DAY)
me_12955	re_1379.00	EX-MODERATE SMOKER (10-19/DAY)
me_12946	re_137F.00	EX-SMOKER - AMOUNT UNKNOWN

me_12961	re_1377.00	EX-TRIVIAL SMOKER (<1/DAY)
me_12959	re_137B.00	EX-VERY HEAVY SMOKER (40+/DAY)
me_101338	re_137m.00	FAILED ATTEMPT TO STOP SMOKING
me_3568	re_1375.00	HEAVY SMOKER - 20-39 CIGS/DAY
me_12964	re_137C.00	KEEPS TRYING TO STOP SMOKING
me_18926	re_67H1.00	LIFESTYLE ADVICE REGARDING SMOKING
me_12944	re_1373.00	LIGHT SMOKER - 1-9 CIGS/DAY
me_62686	re_137h.00	MINUTES FROM WAKING TO FIRST TOBACCO CONSUMPTIO
me_1878	re_1374.00	MODERATE SMOKER - 10-19 CIGS/D
me_47273	re_ZRaM.00	MOTIVES FOR SMOKING SCALE
me_34126	re_13p0.00	NEGOTIATED DATE FOR CESSATION OF SMOKING
me_33	re_1371.00	NEVER SMOKED TOBACCO
me_11788	re_1371.11	NON-SMOKER
me_98177	re_9kn..00	NON-SMOKER ANNUAL REVIEW - ENHANCED SERVICES AD
me_30762	re_137d.00	NOT INTERESTED IN STOPPING SMOKING
me_12941	re_1372.11	OCCASIONAL SMOKER
me_91708	re_745Hy00	OTHER SPECIFIED SMOKING CESSATION THERAPY
me_12947	re_137H.00	PIPE SMOKER
me_12967	re_137a.00	PIPE TOBACCO CONSUMPTION
me_31114	re_137b.00	READY TO STOP SMOKING
me_46321	re_137f.00	REASON FOR RESTARTING SMOKING
me_59866	re_ZRh4.00	REASONS FOR SMOKING SCALE
me_99838	re_137K000	RECENTLY STOPPED SMOKING
me_102361	re_9NS0200	REFERRAL FOR SMOKING CESSATION SERVICE OFFERED
me_98154	re_8HkQ.00	REFERRAL TO NHS STOP SMOKING SERVICE
me_18573	re_8H7i.00	REFERRAL TO SMOKING CESSATION ADVISOR
me_10742	re_8HTK.00	REFERRAL TO STOP-SMOKING CLINIC
me_40418	re_9OO2.00	REFUSES STOP SMOKING MONITOR
me_12945	re_137M.00	ROLLS OWN CIGARETTES
me_11356	re_9N2k.00	SEEN BY SMOKING CESSATION ADVISOR
me_1823	re_137P.11	SMOKER
me_12942	re_137..11	SMOKER - AMOUNT SMOKED
me_16717	re_H310100	SMOKERS' COUGH
me_96992	re_9kc..00	SMOKING CESSATION - ENHANCED SERVICES ADMINISTR
me_7622	re_8CAL.00	SMOKING CESSATION ADVICE
me_41042	re_8CAg.00	SMOKING CESSATION ADVICE PROVIDED BY COMMUNITY
me_94958	re_745H400	SMOKING CESSATION DRUG THERAPY
me_10211	re_13p..00	SMOKING CESSATION MILESTONES
me_38112	re_13p5.00	SMOKING CESSATION PROGRAMME START DATE
me_74907	re_745H.00	SMOKING CESSATION THERAPY
me_90522	re_745Hz00	SMOKING CESSATION THERAPY NOS
me_98493	re_9kc0.00	SMOKING CESSATN MONITOR TEMPLATE COMPLET - ENHA
me_10898	re_13p4.00	SMOKING FREE WEEKS
me_12966	re_137V.00	SMOKING REDUCED
me_12951	re_137Q.11	SMOKING RESTARTED
me_41979	re_137e.00	SMOKING RESTARTED

me_12952	re_137Q.00	SMOKING STARTED
me_34127	re_13p1.00	SMOKING STATUS AT 4 WEEKS
me_34374	re_13p2.00	SMOKING STATUS BETWEEN 4 AND 52 WEEKS
me_32083	re_9OO..11	STOP SMOKING CLINIC ADMIN.
me_98245	re_8HBM.00	STOP SMOKING FACE TO FACE FOLLOW-UP
me_42722	re_9OO4.00	STOP SMOKING MONITOR 1ST LETTR
me_60720	re_9OO5.00	STOP SMOKING MONITOR 2ND LETTR
me_66387	re_9OO6.00	STOP SMOKING MONITOR 3RD LETTR
me_21637	re_9OOZ.00	STOP SMOKING MONITOR ADMIN.NOS
me_40417	re_9OO3.00	STOP SMOKING MONITOR DEFAULT
me_58597	re_9OO8.00	STOP SMOKING MONITOR PHONE INV
me_53101	re_9OO7.00	STOP SMOKING MONITOR VERB.INV.
me_19485	re_9OOA.00	STOP SMOKING MONITOR.CHCK DONE
me_7130	re_9OO..12	STOP SMOKING MONITORING ADMIN.
me_776	re_137K.00	STOPPED SMOKING
me_30423	re_137c.00	THINKING ABOUT STOPPING SMOKING
me_105711	re_137n.00	TOTAL TIME SMOKED
me_12958	re_1372.00	TRIVIAL SMOKER - < 1 CIG/DAY
me_12240	re_137G.00	TRYING TO GIVE UP SMOKING
me_1822	re_1376.00	VERY HEAVY SMOKER - 40+CIGS/D
Race		
me_12350	re_9iC..00	AFRICAN - ETHNIC CATEGORY 2001 CENSUS
me_45125	re_1342.00	AFRICAN ORIGIN
me_25422	re_9i2K.00	ALBANIAN - ETHNIC CATEGORY 2001 CENSUS
me_26455	re_9iFK.00	ANY OTHER GROUP - ETHNIC CATEGORY 2001 CENSUS
me_46059	re_9iF9.00	ARAB - ETHNIC CATEGORY 2001 CENSUS
me_47005	re_9i64.00	ASIAN AND CHINESE - ETHNIC CATEGORY 2001 CENS
me_25801	re_1343.00	ASIAN ORIGIN
me_47975	re_1346.00	AUSTRALIAN ORIGIN
me_12433	re_9i2G.00	BALTIC ESTONIAN/LATVIAN/LITHUANIAN - ETHN CAT
me_24740	re_9S8..00	BANGLADESHI
me_28888	re_9i9..00	BANGLADESHI OR BRITISH BANGLADESHI - ETHN CAT
me_35412	re_9S44.00	BLACK - OTHER AFRICAN COUNTRY
me_35350	re_9S47.00	BLACK - OTHER ASIAN
me_25676	re_9S5..00	BLACK - OTHER, MIXED
me_12778	re_9S3..00	BLACK AFRICAN
me_32443	re_9SB6.00	BLACK AFRICAN AND WHITE
me_12795	re_9i60.00	BLACK AND ASIAN - ETHNIC CATEGORY 2001 CENSUS
me_49940	re_9i61.00	BLACK AND CHINESE - ETHNIC CATEGORY 2001 CENS
me_40110	re_9i62.00	BLACK AND WHITE - ETHNIC CATEGORY 2001 CENSUS
me_57752	re_9S43.12	BLACK ARAB
me_26312	re_9S48.00	BLACK BLACK - OTHER
me_12452	re_9S41.00	BLACK BRITISH
me_40097	re_9iD2.00	BLACK BRITISH - ETHNIC CATEGORY 2001 CENSUS
me_12632	re_9S2..00	BLACK CARIBBEAN
me_47950	re_9S42.11	BLACK CARIBBEAN

me_32425	re_9SB5.00	BLACK CARIBBEAN AND WHITE
me_57435	re_9S42.00	BLACK CARIBBEAN/W.I./GUYANA
me_47965	re_9S45.00	BLACK E AFRIC ASIA/INDO-CARIBB
me_57753	re_9S45.11	BLACK EAST AFRICAN ASIAN
me_32100	re_9S42.13	BLACK GUYANA
me_48005	re_9S46.00	BLACK INDIAN SUB-CONTINENT
me_57763	re_9S45.12	BLACK INDO-CARIBBEAN
me_50286	re_9S43.13	BLACK IRANIAN
me_41329	re_9S43.00	BLACK N AFRICAN/ARAB/IRANIAN
me_46812	re_9S43.11	BLACK NORTH AFRICAN
me_47997	re_9S42.12	BLACK WEST INDIAN
me_24339	re_9S4..00	BLACK, OTHER, NON-MIXED ORIGIN
me_46956	re_9i2L.00	BOSNIAN - ETHNIC CATEGORY 2001 CENSUS
me_32110	re_9SA1.00	BRIT. ETHNIC MINOR. SPEC.(NMO)
me_57764	re_9SA2.00	BRIT. ETHNIC MINOR. UNSP (NMO)
me_12653	re_9iA8.00	BRITISH ASIAN - ETHNIC CATEGORY 2001 CENSUS
me_12351	re_9i0..00	BRITISH OR MIXED BRITISH - ETHNIC CATEGORY 20
me_63872	re_9iF4.00	BUDDHIST - ETHNIC CATEGORY 2001 CENSUS
me_12432	re_9iB..00	CARIBBEAN - ETHNIC CATEGORY 2001 CENSUS
me_32399	re_9iA7.00	CARIBBEAN ASIAN - ETHNIC CATEGORY 2001 CENSUS
me_54593	re_9SA3.00	CARIBBEAN I./W.I./GUYANA (NMO)
me_12718	re_9S9..00	CHINESE
me_24272	re_9T1C.00	CHINESE
me_12468	re_9iE..00	CHINESE - ETHNIC CATEGORY 2001 CENSUS
me_12706	re_9i63.00	CHINESE AND WHITE - ETHNIC CATEGORY 2001 CENS
me_28973	re_9i2H.00	COMMONWEALTH (RUSSIAN) INDEP STATES - ETHN CA
me_28887	re_9i23.00	CORNISH - ETHNIC CATEGORY 2001 CENSUS
me_28866	re_9i2M.00	CROATIAN - ETHNIC CATEGORY 2001 CENSUS
me_32778	re_9i26.00	CYPRIOT (PART NOT STATED) - ETHNIC CATEGORY 2
me_38097	re_9SA6.00	E AFRIC ASIAN/INDO-CARIB (NMO)
me_46818	re_9SA6.11	EAST AFRICAN ASIAN (NMO)
me_47077	re_9iA3.00	EAST AFRICAN ASIAN - ETHNIC CATEGORY 2001 CEN
me_12352	re_9i20.00	ENGLISH - ETHNIC CATEGORY 2001 CENSUS
me_12435	re_9i...00	ETHNIC CATEGORY - 2001 CENSUS
me_12459	re_9iG..00	ETHNIC CATEGORY NOT STATED - 2001 CENSUS
me_12429	re_9SD..00	ETHNIC GROUP NOT GIVEN - PATIENT REFUSED
me_24340	re_9SE..00	ETHNIC GROUP NOT RECORDED
me_10196	re_9S...00	ETHNIC GROUPS (CENSUS)
me_45199	re_9SZ..00	ETHNIC GROUPS (CENSUS) NOS
me_25656	re_1341.00	EUROPEAN ORIGIN
me_47960	re_1349.00	FAR EASTERN ORIGIN
me_12420	re_9iF2.00	FILIPINO - ETHNIC CATEGORY 2001 CENSUS
me_45955	re_9SAA.11	GREEK (NMO)
me_12355	re_9i27.00	GREEK - ETHNIC CATEGORY 2001 CENSUS
me_47949	re_9SAA.12	GREEK CYPRIOT (NMO)
me_12769	re_9i28.00	GREEK CYPRIOT - ETHNIC CATEGORY 2001 CENSUS

me_45947	re_9SAA.00	GREEK/GREEK CYPRIOT (NMO)
me_93144	re_9SA3.13	GUYANA (NMO)
me_42290	re_9i2E.00	GYPSY/ROMANY - ETHNIC CATEGORY 2001 CENSUS
me_56127	re_9iF5.00	HINDU - ETHNIC CATEGORY 2001 CENSUS
me_12482	re_9S6..00	INDIAN
me_25920	re_9T1D.00	INDIAN
me_12414	re_9i7..00	INDIAN OR BRITISH INDIAN - ETHNIC CATEGORY 20
me_45144	re_1347.00	INDIAN ORIGIN
me_99316	re_9SA6.12	INDO-CARIBBEAN (NMO)
me_25082	re_9SA4.12	IRANIAN (NMO)
me_25937	re_9iFD.00	IRANIAN - ETHNIC CATEGORY 2001 CENSUS
me_24270	re_9SA9.00	IRISH (NMO)
me_12532	re_9i1..00	IRISH - ETHNIC CATEGORY 2001 CENSUS
me_47601	re_9SI..00	IRISH TRAVELLER
me_55223	re_9i2C.00	IRISH TRAVELLER - ETHNIC CATEGORY 2001 CENSUS
me_46964	re_9iFC.00	ISRAELI - ETHNIC CATEGORY 2001 CENSUS
me_12412	re_9i2B.00	ITALIAN - ETHNIC CATEGORY 2001 CENSUS
me_12473	re_9iF1.00	JAPANESE - ETHNIC CATEGORY 2001 CENSUS
me_46063	re_9iF6.00	JEWISH - ETHNIC CATEGORY 2001 CENSUS
me_64133	re_9iA2.00	KASHMIRI - ETHNIC CATEGORY 2001 CENSUS
me_26341	re_9i2J.00	KOSOVAN - ETHNIC CATEGORY 2001 CENSUS
me_45964	re_9iFE.00	KURDISH - ETHNIC CATEGORY 2001 CENSUS
me_26246	re_9iFG.00	LATIN AMERICAN - ETHNIC CATEGORY 2001 CENSUS
me_12730	re_9iF3.00	MALAYSIAN - ETHNIC CATEGORY 2001 CENSUS
me_47951	re_1348.00	MIDDLE EASTERN ORIGIN
me_46056	re_9iA9.00	MIXED ASIAN - ETHNIC CATEGORY 2001 CENSUS
me_40096	re_9iD3.00	MIXED BLACK - ETHNIC CATEGORY 2001 CENSUS
me_26391	re_9i2Q.00	MIXED IRISH AND OTHER WHITE - ETHNIC CATEGORY
me_25451	re_9iFF.00	MOROCCAN - ETHNIC CATEGORY 2001 CENSUS
me_47091	re_9iF7.00	MUSLIM - ETHNIC CATEGORY 2001 CENSUS
me_24962	re_9SA4.00	N AFRICAN ARAB/IRANIAN (NMO)
me_32886	re_9iD1.00	NIGERIAN - ETHNIC CATEGORY 2001 CENSUS
me_47028	re_9iFA.00	NORTH AFRICAN - ETHNIC CATEGORY 2001 CENSUS
me_47285	re_9SA4.11	NORTH AFRICAN ARAB (NMO)
me_41150	re_1344.00	NORTH AMERICAN ORIGIN
me_42294	re_9i24.00	NORTHERN IRISH - ETHNIC CATEGORY 2001 CENSUS
me_12402	re_9i2R.00	OTH WHITE EUROPEAN/EUROPEAN UNSP/MIXED EUROPE
me_12434	re_9iF..00	OTHER - ETHNIC CATEGORY 2001 CENSUS
me_26379	re_9SA8.00	OTHER ASIAN (NMO)
me_12513	re_9iA..00	OTHER ASIAN BACKGROUND - ETHNIC CATEGORY 2001
me_12668	re_9SH..00	OTHER ASIAN ETHNIC GROUP
me_28935	re_9iAA.00	OTHER ASIAN OR ASIAN UNSPECIFIED ETHNIC CATEG
me_32165	re_9S52.00	OTHER BLACK - BLACK/ASIAN ORIG
me_25623	re_9S51.00	OTHER BLACK - BLACK/WHITE ORIG
me_32389	re_9iD..00	OTHER BLACK BACKGROUND - ETHNIC CATEGORY 2001
me_32136	re_9SG..00	OTHER BLACK ETHNIC GROUP

me_46047	re_9iD4.00	OTHER BLACK OR BLACK UNSPECIFIED ETHNIC CATEG
me_12757	re_9SJ..00	OTHER ETHNIC GROUP
me_41214	re_9SAD.00	OTHER ETHNIC NEC (NMO)
me_30280	re_9SA..00	OTHER ETHNIC NON-MIXED (NMO)
me_32401	re_9SB2.00	OTHER ETHNIC, ASIAN/WHITE ORIG
me_47401	re_9SB1.00	OTHER ETHNIC, BLACK/WHITE ORIG
me_12696	re_9SB..00	OTHER ETHNIC, MIXED ORIGIN
me_35459	re_9SB3.00	OTHER ETHNIC, MIXED WHITE ORIG
me_32420	re_9SB4.00	OTHER ETHNIC, OTHER MIXED ORIG
me_12633	re_9SAC.00	OTHER EUROPEAN (NMO)
me_12873	re_9i6..00	OTHER MIXED BACKGROUND - ETHNIC CATEGORY 2001
me_32408	re_9i65.00	OTHER MIXED OR MIXED UNSPECIFIED ETHNIC CATEG
me_28900	re_9i2S.00	OTHER MIXED WHITE - ETHNIC CATEGORY 2001 CENS
me_28936	re_9i2P.00	OTHER REPUBLICS FORMER YUGOSLAVIA - ETHNIC CA
me_12421	re_9i2..00	OTHER WHITE BACKGROUND - ETHNIC CATEGORY 2001
me_26310	re_9S14.00	OTHER WHITE BRITISH ETHNIC GROUP
me_12444	re_9S12.00	OTHER WHITE ETHNIC GROUP
me_12591	re_9i2T.00	OTHER WHITE OR WHITE UNSPECIFIED ETHNIC CATEG
me_24690	re_9S7..00	PAKISTANI
me_12460	re_9i8..00	PAKISTANI OR BRITISH PAKISTANI - ETHNIC CATEG
me_12467	re_9i2F.00	POLISH - ETHNIC CATEGORY 2001 CENSUS
me_26392	re_9iA1.00	PUNJABI - ETHNIC CATEGORY 2001 CENSUS
me_25894	re_134H.00	RACE: AFRO-CARIBBEAN
me_45167	re_134L.00	RACE: AFRO-CAUCASIAN
me_12875	re_134C.00	RACE: ARAB
me_26348	re_134I.00	RACE: BANGLADESHI
me_12191	re_134B.00	RACE: CAUCASIAN
me_32224	re_134D.00	RACE: CHINESE
me_45163	re_134E.00	RACE: JAPANESE
me_41394	re_134F.00	RACE: KOREAN
me_30408	re_134J.00	RACE: MIXED
me_46137	re_134P.00	RACE: NOT STATED
me_41200	re_134G.00	RACE: ORIENTAL
me_32391	re_134P.11	RACE: OTHER
me_26062	re_134M.00	RACE: PAKISTANI
me_22953	re_134O.00	RACE: UNKNOWN
me_32095	re_134K.00	RACE: WEST INDIAN
me_25550	re_134N.00	RACE: WHITE
me_12436	re_9i21.00	SCOTTISH - ETHNIC CATEGORY 2001 CENSUS
me_47074	re_9i2N.00	SERBIAN - ETHNIC CATEGORY 2001 CENSUS
me_49658	re_9iF8.00	SIKH - ETHNIC CATEGORY 2001 CENSUS
me_12887	re_9iA6.00	SINHALESE - ETHNIC CATEGORY 2001 CENSUS
me_12443	re_9iD0.00	SOMALI - ETHNIC CATEGORY 2001 CENSUS
me_32101	re_1345.00	SOUTH AMERICAN ORIGIN
me_12756	re_9iFH.00	SOUTH AND CENTRAL AMERICAN - ETHNIC CATEGORY
me_12608	re_9iA4.00	SRI LANKAN - ETHNIC CATEGORY 2001 CENSUS

me_12760	re_9iA5.00	TAMIL - ETHNIC CATEGORY 2001 CENSUS
me_55113	re_9i2D.00	TRAVELLER - ETHNIC CATEGORY 2001 CENSUS
me_32126	re_9SAB.11	TURKISH (NMO)
me_12746	re_9i29.00	TURKISH - ETHNIC CATEGORY 2001 CENSUS
me_32069	re_9SAB.12	TURKISH CYPRIOT (NMO)
me_32413	re_9i2A.00	TURKISH CYPRIOT - ETHNIC CATEGORY 2001 CENSUS
me_32066	re_9SAB.00	TURKISH/TURKISH CYPRIOT (NMO)
me_40102	re_9i25.00	ULSTER SCOTS - ETHNIC CATEGORY 2001 CENSUS
me_25411	re_9SC..00	VIETNAMESE
me_12719	re_9iF0.00	VIETNAMESE - ETHNIC CATEGORY 2001 CENSUS
me_12681	re_9i22.00	WELSH - ETHNIC CATEGORY 2001 CENSUS
me_57075	re_9SA3.12	WEST INDIAN (NMO)
me_45131	re_134A.00	WEST INDIAN ORIGIN
me_22467	re_9S1..00	WHITE
me_12638	re_9i5..00	WHITE AND ASIAN - ETHNIC CATEGORY 2001 CENSUS
me_12437	re_9i4..00	WHITE AND BLACK AFRICAN - ETHNIC CATEGORY 200
me_12742	re_9i3..00	WHITE AND BLACK CARIBBEAN - ETHNIC CATEGORY 2
me_12446	re_9S10.00	WHITE BRITISH
me_98111	re_9i00.00	WHITE BRITISH - ETHNIC CATEGORY 2001 CENSUS
me_24837	re_9S11.00	WHITE IRISH
me_98213	re_9i10.00	WHITE IRISH - ETHNIC CATEGORY 2001 CENSUS
me_26467	re_9S13.00	WHITE SCOTTISH
Hypertension		
me_36119	re_F421111	ARTEROSCLEROTIC RETINOPATHY
me_34455	re_F421112	ATHEROSCLERITIC RETINOPATHY
me_41229	re_F421100	ATHEROSCLEROTIC RETINOPATHY
me_1894	re_G201.00	BENIGN ESSENTIAL HYPERTENSION
me_8732	re_G2...11	BP - HYPERTENSIVE DISEASE
me_799	re_G20..00	ESSENTIAL HYPERTENSION
me_10818	re_G20z.00	ESSENTIAL HYPERTENSION NOS
me_2666	re_14A2.00	H/O: HYPERTENSION
me_351	re_G20..11	HIGH BLOOD PRESSURE
me_3712	re_G20z.11	HYPERTENSION NOS
me_31341	re_G24z100	HYPERTENSION SECONDARY TO DRUG
me_34744	re_G244.00	HYPERTENSION SECONDARY TO ENDOCRINE DISORDERS
me_21826	re_662F.00	HYPERTENSION TREATM. STARTED
me_204	re_G2...00	HYPERTENSIVE DISEASE
me_7057	re_G2z..00	HYPERTENSIVE DISEASE NOS
me_15106	re_G22z.00	HYPERTENSIVE RENAL DISEASE NOS
me_15377	re_G200.00	MALIGNANT ESSENTIAL HYPERTENSION
me_107704	re_G200.99	PRIMARY HYPERTENSION
me_5513	re_G20..12	REFERRAL TO HYPERTENSION CLINIC
me_29310	re_8HT5.00	RENAL HYPERTENSION
me_57288	re_G22z.11	SECONDARY BENIGN HYPERTENSION
me_51635	re_G241.00	SECONDARY BENIGN HYPERTENSION NOS
me_7329	re_G241z00	SECONDARY HYPERTENSION

me_16059	re_G24..00	SECONDARY HYPERTENSION NOS
me_42229	re_G24z.00	SECONDARY HYPERTENSION NOS
me_31755	re_G24zz00	SECONDARY MALIGNANT HYPERTENSION
me_73293	re_G240.00	SECONDARY MALIGNANT HYPERTENSION NOS
me_31387	re_G240z00	SECONDARY RENOVASCULAR HYPERTENSION NOS
me_27634	re_G24z000	SEEN IN HYPERTENSION CLINIC
me_4344	re_9N03.00	SEEN IN HYPERTENSION CLINIC
me_4372	re_9N1y200	SYSTOLIC HYPERTENSION
me_97533	re_G202.00	[X]HYPERTENSION SECONDARY TO OTHER RENAL DISORDERS
me_102458	re_Gyu2100	[X]OTHER SECONDARY HYPERTENSION
	re_Gyu2000	
Skin Ulcers		
me_14995	re_M270.11	BED SORE
me_9180	re_M27..00	CHRONIC SKIN ULCER
me_3929	re_M27z.00	CHRONIC SKIN ULCER NOS
me_24232	re_M27y.00	CHRONIC ULCER OF SKIN, OTHER SPECIFIED SITES
me_6862	re_M270.00	DECUBITUS (PRESSURE) ULCER
me_108537	re_M270.14	DECUBITUS ULCER AND PRESSURE AREA
me_15506	re_M270.99	DRESSING OF SKIN ULCER NEC
me_6654	re_7G2E500	DRESSING OF ULCER
me_5057	re_81H1.00	FOOT ULCER
	re_M271.11	
me_5961	re_14F3.00	H/O: CHRONIC SKIN ULCER
me_12704	re_G835.00	INFECTED VARICOSE ULCER
me_6308	re_M271.12	ISCHAEMIC LEG ULCER
me_24327	re_M271000	ISCHAEMIC ULCER DIABETIC FOOT
	re_M271.99	LEG ULCER
me_1216	re_M271.13	LEG ULCER NOS
me_9881	re_M271200	MIXED DIABETIC ULCER - FOOT
me_32006	re_M271.14	NEUROGENIC LEG ULCER
me_11663	re_M271100	NEUROPATHIC DIABETIC ULCER - FOOT
me_34912	re_C109400	NON-INSULIN DEPENDENT DIABETES MELLITUS WITH ULCER
me_3928	re_M271.00	NON-PRESSURE ULCER LOWER LIMB
me_6207	re_2FF..00	O/E - SKIN ULCER
me_29007	re_2FFZ.00	O/E - SKIN ULCER NOS
me_1727	re_2FF2.00	O/E - SKIN ULCER PRESENT
me_46101	re_M270.12	PLASTER ULCER
me_4929	re_M270.13	PRESSURE SORE
me_4487	re_4JG3.00	SKIN ULCER SWAB TAKEN
me_14838	re_M271.15	TROPHIC LEG ULCER
me_65704	re_C109412	TYPE 2 DIABETES MELLITUS WITH ULCER
me_55075	re_C109411	TYPE II DIABETES MELLITUS WITH ULCER
	re_G832.99	VARICOSE ULCER + INFLAMMATION
	re_G830.99	VARICOSE ULCER OF LEG
	re_G837.99	VARICOSE ULCER OF LEG
me_1913	re_G830.00	VARICOSE VEINS OF THE LEG WITH ULCER

me_16079	re_G832.00	VARICOSE VEINS OF THE LEG WITH ULCER AND ECZEMA
Autoimmune disease		
me_47831	re_N043100	ACUTE POLYARTICULAR JUVENILE RHEUMATOID ARTHRITIS
me_32001	re_N04y200	ADULT-ONSET STILL'S DISEASE
me_96291	re_F204.00	BENIGN MULTIPLE SCLEROSIS
me_3944	re_N044.00	CHRONIC POST-RHEUMATIC ARTHROPATHY
me_17675	re_N001100	CREST SYNDROME
me_6538	re_J401z11	CROHN'S COLITIS
me_593	re_J40..11	CROHN'S DISEASE
me_59994	re_J40z.11	CROHN'S DISEASE NOS
me_39278	re_J400400	CROHN'S DISEASE OF THE ILEUM NOS
me_66238	re_J400300	CROHN'S DISEASE OF THE ILEUM UNSPECIFIED
me_20688	re_J401z00	CROHN'S DISEASE OF THE LARGE BOWEL NOS
me_9359	re_J400z00	CROHN'S DISEASE OF THE SMALL BOWEL NOS
me_28476	re_J400200	CROHN'S DISEASE OF THE TERMINAL ILEUM
me_4908	re_N003.00	DERMATOMYOSITIS
me_28316	re_N003X00	DERMATOPOLYMYOSITIS, UNSPECIFIED
me_2667	re_M154100	DISCOID LUPUS ERYTHEMATOSUS
me_39037	re_J401200	EXACERBATION OF CROHN'S DISEASE OF LARGE INTESTINE
me_36913	re_J400500	EXACERBATION OF CROHN'S DISEASE OF SMALL INTESTINE
me_2298	re_F203.00	EXACERBATION OF MULTIPLE SCLEROSIS
me_22516	re_J410400	EXACERBATION OF ULCERATIVE COLITIS
me_23552	re_N041.00	FELTY'S SYNDROME
me_37418	re_N241200	FIBROMYOSITIS NOS
me_8350	re_N040T00	FLARE OF RHEUMATOID ARTHRITIS
me_23730	re_F202.00	GENERALISED MULTIPLE SCLEROSIS
me_51578	re_J40..12	GRANULOMATOUS ENTERITIS
me_5133	re_J41..00	IDIOPATHIC PROCTOCOLITIS
me_15207	re_J41z.00	IDIOPATHIC PROCTOCOLITIS NOS
me_20615	re_N04..11	INFLAMMATORY POLYARTHROPATHY
me_24747	re_N04z.00	INFLAMMATORY POLYARTHROPATHY NOS
me_34880	re_N10..00	INFLAMMATORY SPONDYLOPATHIES
me_42405	re_N045000	JUVENILE ANKYLOSING SPONDYLITIS
me_12575	re_N045300	JUVENILE ARTHRITIS IN CROHN'S DISEASE
me_28456	re_N045200	JUVENILE ARTHRITIS IN PSORIASIS
me_71083	re_N045400	JUVENILE ARTHRITIS IN ULCERATIVE COLITIS
me_32649	re_N003000	JUVENILE DERMATOMYOSITIS
me_31360	re_N045500	JUVENILE RHEUMATOID ARTHRITIS
me_4186	re_N043.00	JUVENILE RHEUMATOID ARTHRITIS - STILL'S DISEASE
me_27557	re_N043z00	JUVENILE RHEUMATOID ARTHRITIS NOS
me_50644	re_N043000	JUVENILE RHEUMATOID ARTHROPATHY UNSPECIFIED
me_31181	re_N045100	JUVENILE SERONEGATIVE POLYARTHRITIS
me_4125	re_M154.00	LUPUS ERYTHEMATOSUS
me_7522	re_M154z00	LUPUS ERYTHEMATOSUS NOS
me_36276	re_N043300	MONARTICULAR JUVENILE RHEUMATOID ARTHRITIS
me_23950	re_J41..11	MUCOUS COLITIS AND/OR PROCTITIS

me_684	re_F20..00	MULTIPLE SCLEROSIS
me_50161	re_8CS1.00	MULTIPLE SCLEROSIS CARE PLAN AGREED
me_43232	re_666B.00	MULTIPLE SCLEROSIS MULTIDISCIPLINARY REVIEW
me_20493	re_F20z.00	MULTIPLE SCLEROSIS NOS
me_40344	re_F200.00	MULTIPLE SCLEROSIS OF THE BRAIN STEM
me_69886	re_F201.00	MULTIPLE SCLEROSIS OF THE SPINAL CORD
me_44985	re_666A.00	MULTIPLE SCLEROSIS REVIEW
me_27512	re_N241.00	MYALGIA AND MYOSITIS UNSPECIFIED
me_3649	re_N241z00	MYALGIA OR MYOSITIS NOS
me_5492	re_N241100	MYOSITIS UNSPECIFIED
me_29616	re_J08z900	OROFACIAL CROHN'S DISEASE
me_24550	re_J41y.00	OTHER IDIOPATHIC PROCTOCOLITIS
me_43090	re_J41yz00	OTHER IDIOPATHIC PROCTOCOLITIS NOS
me_7196	re_N045.00	OTHER JUVENILE ARTHRITIS
me_49227	re_N042.00	OTHER RHEUMATOID ARTHROPATHY + VISCERAL/SYSTEMIC INVOLVEMENT
me_36597	re_N04y.00	OTHER SPECIFIED INFLAMMATORY POLYARTHROPATHY
me_23833	re_N04yz00	OTHER SPECIFIED INFLAMMATORY POLYARTHROPATHY NOS
me_21533	re_N043200	PAUCIARTICULAR JUVENILE RHEUMATOID ARTHRITIS
me_46622	re_N045600	PAUCIARTICULAR ONSET JUVENILE CHRONIC ARTHRITIS
me_1408	re_N20..00	POLYMYALGIA RHEUMATICA
me_15511	re_N004.00	POLYMYOSITIS
me_96607	re_F206.00	PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS
me_44141	re_N001000	PROGRESSIVE SYSTEMIC SCLEROSIS
me_26368	re_M160000	PSORIASIS SPONDYLITICA
me_96880	re_M160.11	PSORIATIC ARTHRITIS
me_476	re_M160.00	PSORIATIC ARTHROPATHY
me_12500	re_M160z00	PSORIATIC ARTHROPATHY NOS
me_11286	re_J40..00	REGIONAL ENTERITIS - CROHN'S DISEASE
me_52449	re_J40z.00	REGIONAL ENTERITIS NOS
me_62628	re_J401000	REGIONAL ENTERITIS OF THE COLON
me_71945	re_J400000	REGIONAL ENTERITIS OF THE DUODENUM
me_63036	re_J400100	REGIONAL ENTERITIS OF THE JEJUNUM
me_44426	re_J401.00	REGIONAL ENTERITIS OF THE LARGE BOWEL
me_64773	re_J401100	REGIONAL ENTERITIS OF THE RECTUM
me_51576	re_J400.00	REGIONAL ENTERITIS OF THE SMALL BOWEL
me_15773	re_J402.00	REGIONAL ILEOCOLITIS
me_95972	re_F207.00	RELAPSING AND REMITTING MULTIPLE SCLEROSIS
me_8583	re_N042000	RHEUMATIC CARDITIS
me_844	re_N040.00	RHEUMATOID ARTHRITIS
me_31054	re_N040S00	RHEUMATOID ARTHRITIS - MULTIPLE JOINT
me_27603	re_N04..00	RHEUMATOID ARTHRITIS AND OTHER INFLAMMATORY POLYARTHROPATHY
me_51238	re_N040K00	RHEUMATOID ARTHRITIS OF 1ST MTP JOINT
me_100914	re_N040400	RHEUMATOID ARTHRITIS OF ACROMIOCLAVICULAR JOINT
me_51239	re_N040F00	RHEUMATOID ARTHRITIS OF ANKLE
me_63198	re_N040A00	RHEUMATOID ARTHRITIS OF DIP JOINT OF FINGER

me_63365	re_N040600	RHEUMATOID ARTHRITIS OF DISTAL RADIO-ULNAR JOINT
me_59738	re_N040500	RHEUMATOID ARTHRITIS OF ELBOW
me_49067	re_N040B00	RHEUMATOID ARTHRITIS OF HIP
me_107112	re_N040M00	RHEUMATOID ARTHRITIS OF IP JOINT OF TOE
me_50863	re_N040D00	RHEUMATOID ARTHRITIS OF KNEE
me_99414	re_N040L00	RHEUMATOID ARTHRITIS OF LESSER MTP JOINT
me_42299	re_N040800	RHEUMATOID ARTHRITIS OF MCP JOINT
me_71784	re_N040J00	RHEUMATOID ARTHRITIS OF OTHER TARSAL JOINT
me_41941	re_N040900	RHEUMATOID ARTHRITIS OF PIP JOINT OF FINGER
me_100776	re_N040C00	RHEUMATOID ARTHRITIS OF SACRO-ILIAC JOINT
me_21358	re_N040200	RHEUMATOID ARTHRITIS OF SHOULDER
me_107963	re_N040300	RHEUMATOID ARTHRITIS OF STERNOCLAVICULAR JOINT
me_73619	re_N040G00	RHEUMATOID ARTHRITIS OF SUBTALAR JOINT
me_70658	re_N040H00	RHEUMATOID ARTHRITIS OF TALONAVICULAR JOINT
me_107791	re_N040E00	RHEUMATOID ARTHRITIS OF TIBIO-FIBULAR JOINT
me_48832	re_N040700	RHEUMATOID ARTHRITIS OF WRIST
me_37431	re_N042z00	RHEUMATOID ARTHROPATHY + VISCERAL/SYSTEMIC INVOLVEMENT NOS
me_18155	re_N040Q00	RHEUMATOID BURSITIS
me_31724	re_H570.00	RHEUMATOID LUNG
me_9954	re_N04y000	RHEUMATOID LUNG
me_46436	re_N042100	RHEUMATOID LUNG DISEASE
me_53621	re_N040R00	RHEUMATOID NODULE
me_5723	re_N042200	RHEUMATOID NODULE
me_30548	re_N040N00	RHEUMATOID VASCULITIS
me_96246	re_F208.00	SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS
me_4578	re_N04y100	SERO NEGATIVE ARTHRITIS
me_6916	re_N040P00	SERONEGATIVE RHEUMATOID ARTHRITIS
me_9707	re_N047.00	SEROPOSITIVE ERROSIVE RHEUMATOID ARTHRITIS
me_12019	re_N04X.00	SEROPOSITIVE RHEUMATOID ARTHRITIS, UNSPECIFIED
me_25390	re_M154700	SUBACUTE CUTANEOUS LUPUS ERYTHEMATOSUS
me_7871	re_N000.00	SYSTEMIC LUPUS ERYTHEMATOSUS
me_28417	re_N001.12	SYSTEMIC SCLEROSIS
me_30433	re_J411.00	ULCERATIVE (CHRONIC) ENTEROCOLITIS
me_42822	re_J412.00	ULCERATIVE (CHRONIC) ILEOCOLITIS
me_704	re_J410100	ULCERATIVE COLITIS
me_1784	re_J41..12	ULCERATIVE COLITIS AND/OR PROCTITIS
me_48732	re_J410000	ULCERATIVE ILEOCOLITIS
me_104259	re_J413.00	ULCERATIVE PANCOLITIS
me_8347	re_J410300	ULCERATIVE PROCTITIS
me_6650	re_J410.00	ULCERATIVE PROCTOCOLITIS
me_33456	re_J410z00	ULCERATIVE PROCTOCOLITIS NOS
me_24858	re_J410200	ULCERATIVE RECTOSIGMOIDITIS
me_25020	re_N065.00	UNSPECIFIED POLYARTHROPATHY OR POLYARTHRITIS
me_69959	re_Jyu4000	[X]OTHER CROHN'S DISEASE
me_94854	re_Nyu1500	[X]OTHER JUVENILE ARTHRITIS
me_53743	re_Jyu4100	[X]OTHER ULCERATIVE COLITIS

Coronary Heart Disease		
me_91774	re_G341300	ACQUIRED ATRIOVENTRICULAR FISTULA OF HEART
me_40429	re_G301000	ACUTE ANTEROAPICAL INFARCTION
me_12139	re_G300.00	ACUTE ANTEROLATERAL INFARCTION
me_17872	re_G301100	ACUTE ANTEROSEPTAL INFARCTION
me_28736	re_G30y000	ACUTE ATRIAL INFARCTION
me_9276	re_G31y000	ACUTE CORONARY INSUFFICIENCY
me_11983	re_G311500	ACUTE CORONARY SYNDROME
me_8935	re_G31y099	ACUTE INFEROLATERAL INFARCTION
me_29643	re_G302.00	ACUTE INFEROPOSTERIOR INFARCTION
me_241	re_G303.00	ACUTE MYOCARDIAL INFARCTION
me_14658	re_G30..00	ACUTE MYOCARDIAL INFARCTION NOS
me_9507	re_G30z.00	ACUTE NON-Q WAVE INFARCTION
me_10562	re_G307000	ACUTE NON-ST SEGMENT ELEVATION MYOCARDIAL INFARCTION
me_62626	re_G307100	ACUTE PAPILLARY MUSCLE INFARCTION
me_32854	re_G30y100	ACUTE POSTEROLATERAL MYOCARDIAL INFARCTION
me_30330	re_G30B.00	ACUTE Q-WAVE INFARCT
me_41221	re_G309.00	ACUTE SEPTAL INFARCTION
me_12229	re_G30y200	ACUTE ST SEGMENT ELEVATION MYOCARDIAL INFARCTION
me_3704	re_G30X000	ACUTE SUBENDOCARDIAL INFARCTION
me_29758	re_G307.00	ACUTE TRANSMURAL MYOCARDIAL INFARCTION OF UNSPECIF SITE
me_32651	re_G30X.00	ALLOGRAFT BYPASS OF CORONARY ARTERY
me_31556	re_7922.11	ALLOGRAFT REPLACEMENT OF CORONARY ARTERY
me_48767	re_7922.00	ALLOGRAFT REPLACEMENT OF CORONARY ARTERY NOS
me_45370	re_7922z00	ALLOGRAFT REPLACEMENT OF FOUR OR MORE CORONARY ARTERIES
me_70111	re_7922300	ALLOGRAFT REPLACEMENT OF ONE CORONARY ARTERY
me_45886	re_7922000	ALLOGRAFT REPLACEMENT OF THREE CORONARY ARTERIES
me_57241	re_7922200	ALLOGRAFT REPLACEMENT OF TWO CORONARY ARTERIES
me_59193	re_7922100	ANEURYSM OF CORONARY VESSELS
me_6331	re_G341200	ANEURYSM OF HEART
me_41677	re_G341.00	ANEURYSM OF HEART NOS
me_17307	re_G341z00	ANGINA AT REST
me_19655	re_G311.14	ANGINA AT REST
me_20095	re_G311200	ANGINA DECUBITUS
me_29902	re_G330.00	ANGINA DECUBITUS NOS
me_1414	re_G330z00	ANGINA ON EFFORT
me_1430	re_G33z300	ANGINA PECTORIS
me_25842	re_G33..00	ANGINA PECTORIS NOS
me_28554	re_G33z.00	ANGINA PECTORIS NOS
me_14897	re_G33zz00	ANTERIOR MYOCARDIAL INFARCTION NOS
me_18889	re_G301z00	ASYMPTOMATIC CORONARY HEART DISEASE
me_36609	re_G34z000	ATHEROSCLEROTIC CARDIOVASCULAR DISEASE
me_23708	re_G342.00	ATRIAL SEPTAL DEFECT/CURR COMP FOLOW ACUT MYOCARDAL INFARCT
me_13566	re_G361.00	ATTACK - HEART

me_42708	re_G30..11	AUTOGRAFT REPLACEMENT OF FOUR OF MORE CORONARY ARTERIES NEC
me_44561	re_7921300	AUTOGRAFT REPLACEMENT OF ONE CORONARY ARTERY NEC
me_10209	re_7921000	AUTOGRAFT REPLACEMENT OF THREE CORONARY ARTERIES NEC
me_19413	re_7921200	AUTOGRAFT REPLACEMENT OF TWO CORONARY ARTERIES NEC
me_27484	re_7921100	CARDIAC ANEURYSM
me_30421	re_G341.11	CARDIAC RUPTURE FOLLOWING MYOCARDIAL INFARCTION (MI)
me_8568	re_G30..13	CARDIAC SYNDROME X
me_36423	re_G37..00	CERTAIN CURRENT COMPLICATION FOLLOW ACUTE MYOCARDIAL INFARCT
me_24540	re_G36..00	CHRONIC CORONARY INSUFFICIENCY
me_23078	re_G34y000	CHRONIC MYOCARDIAL ISCHAEMIA
me_37682	re_G34y100	CONNECTION OF MAMMARY ARTERY TO CORONARY ARTERY
me_56990	re_7925.00	CONNECTION OF MAMMARY ARTERY TO CORONARY ARTERY NOS
me_37719	re_7925z00	CONNECTION OF MAMMARY ARTERY TO CORONARY ARTERY OS
me_96804	re_7925y00	CONNECTION OF OTHER THORACIC ARTERY TO CORONARY ARTERY
me_72780	re_7926.00	CONNECTION OF OTHER THORACIC ARTERY TO CORONARY ARTERY NOS
me_12734	re_7926z00	CORONARY ARTERY BYPASS GRAFT OCCLUSION
me_737	re_SP07600	CORONARY ARTERY BYPASS GRAFT OPERATIONS
me_1344	re_792..11	CORONARY ARTERY DISEASE
me_5904	re_G340.12	CORONARY ARTERY OPERATIONS
me_10603	re_792..00	CORONARY ARTERY OPERATIONS NOS
me_36854	re_792z.00	CORONARY ARTERY SPASM
me_5413	re_G332.00	CORONARY ATHEROSCLEROSIS
me_105479	re_G340.00	CORONARY MICROVASCULAR DISEASE
me_2491	re_G39..00	CORONARY THROMBOSIS
me_39449	re_G30..12	CORONARY THROMBOSIS NOT RESULTING IN MYOCARDIAL INFARCTION
me_28837	re_G30..98	CREATION OF BYPASS FROM MAMMARY ARTERY TO CORONARY ARTERY
me_4656	re_G312.00	CRESCENDO ANGINA
me_61248	re_7925.11	DIAGNOSTIC TRANSLUMINAL OPERATION ON CORONARY ARTERY NOS
me_56905	re_G311.11	DIAGNOSTIC TRANSLUMINAL OPERATION ON CORONARY ARTERY OS
me_34965	re_792Az00	DIAGNOSTIC TRANSLUMINAL OPERATIONS ON CORONARY ARTERY
me_62608	re_792Ay00	DOUBLE ANASTOM THORACIC ARTERIES TO CORONARY ARTERIES NEC
me_33718	re_792A.00	DOUBLE ANASTOMOSIS OF MAMMARY ARTERIES TO CORONARY ARTERIES
me_5254	re_7926000	DOUBLE CORONARY VESSEL DISEASE
me_31519	re_7925000	DOUBLE IMPLANT OF MAMMARY ARTERIES INTO CORONARY ARTERIES
me_15661	re_G340100	DRESSLER'S SYNDROME
me_22020	re_7925100	ENDARTERECTOMY OF CORONARY ARTERY NEC
me_51702	re_G310.11	EXPLORATION OF CORONARY ARTERY
me_57062	re_792B000	H/O: ANGINA IN LAST YEAR

me_6336	re_7927400	H/O: ANGINA PECTORIS
me_35674	re_14AJ.00	H/O: MYOCARDIAL INFARCT <60
me_40399	re_14A5.00	H/O: MYOCARDIAL INFARCT >60
me_50372	re_14A3.00	H/O: MYOCARDIAL INFARCTION IN LAST YEAR
me_24126	re_14A4.00	HAEMOPERICARDIUM/CURRENT COMP FOLOW ACUT MYOCARD INFARCT
me_16408	re_14AH.00	HEALED MYOCARDIAL INFARCTION
me_1204	re_G360.00	HEART ATTACK
me_1792	re_G32..11	IHD - ISCHAEMIC HEART DISEASE
me_39655	re_G30..14	IMPENDING INFARCTION
me_1678	re_G3...13	INFERIOR MYOCARDIAL INFARCTION NOS
me_8942	re_G311.12	INSERTION OF CORONARY ARTERY STENT
me_42304	re_G308.00	INSERTION OF DRUG-ELUTING CORONARY ARTERY STENT
me_7320	re_7929400	ISCHAEMIC CARDIOMYOPATHY
me_32450	re_7929500	ISCHAEMIC CHEST PAIN
me_240	re_G343.00	ISCHAEMIC HEART DISEASE
me_1676	re_G33z400	ISCHAEMIC HEART DISEASE NOS
me_14898	re_G3...00	LATERAL MYOCARDIAL INFARCTION NOS
me_48822	re_G3z..00	LIMA SEQUENTIAL ANASTOMOSIS
me_22647	re_G305.00	LIMA SINGLE ANASTOMOSIS
me_1677	re_7925011	MI - ACUTE MYOCARDIAL INFARCTION
me_55137	re_7925311	MI - MYOCARDIAL INFARCTION ABORTED
me_68357	re_G30..15	MICROINFARCTION OF HEART
me_105250	re_G311011	MURAL CARDIAC ANEURYSM
me_17133	re_G31y100	MURAL THROMBOSIS
me_26863	re_G341111	NEW ONSET ANGINA
me_18125	re_G30A.00	NOCTURNAL ANGINA
me_4017	re_G33z600	OLD MYOCARDIAL INFARCTION
me_5744	re_G330000	OPEN ANGIOPLASTY OF CORONARY ARTERY
me_27951	re_G32..00	OTHER ACUTE AND SUBACUTE ISCHAEMIC HEART DISEASE
me_9413	re_7927500	OTHER ACUTE AND SUBACUTE ISCHAEMIC HEART DISEASE
me_27977	re_G31..00	OTHER ACUTE AND SUBACUTE ISCHAEMIC HEART DISEASE NOS
me_34803	re_G31y.00	OTHER ACUTE MYOCARDIAL INFARCTION
me_46017	re_G31yz00	OTHER ACUTE MYOCARDIAL INFARCTION NOS
me_7134	re_G30y.00	OTHER AUTOGRAFT BYPASS OF CORONARY ARTERY
me_9414	re_G30yz00	OTHER AUTOGRAFT REPLACEMENT OF CORONARY ARTERY
me_7609	re_7921.11	OTHER AUTOGRAFT REPLACEMENT OF CORONARY ARTERY NOS
me_61310	re_7921.00	OTHER AUTOGRAFT REPLACEMENT OF CORONARY ARTERY OS
me_34963	re_7921z00	OTHER BYPASS OF CORONARY ARTERY
me_33471	re_7921y00	OTHER BYPASS OF CORONARY ARTERY NOS
me_67087	re_792D.00	OTHER CARDIAC WALL ANEURYSM
me_28138	re_792Dz00	OTHER CHRONIC ISCHAEMIC HEART DISEASE
me_15754	re_G341100	OTHER CHRONIC ISCHAEMIC HEART DISEASE NOS
me_41757	re_G34..00	OTHER OPEN OPERATION ON CORONARY ARTERY NOS
me_47788	re_G34z.00	OTHER OPEN OPERATIONS ON CORONARY ARTERY

me_55598	re_7927z00	OTHER REPLACEMENT OF CORONARY ARTERY
me_59423	re_7927.00	OTHER SPECIFIED ALLOGRAFT REPLACEMENT OF CORONARY ARTERY
me_5387	re_792C.00	OTHER SPECIFIED ANTERIOR MYOCARDIAL INFARCTION
me_34633	re_7922y00	OTHER SPECIFIED CHRONIC ISCHAEMIC HEART DISEASE
me_35713	re_G301.00	OTHER SPECIFIED CHRONIC ISCHAEMIC HEART DISEASE NOS
me_22383	re_G34y.00	OTHER SPECIFIED ISCHAEMIC HEART DISEASE
me_31571	re_G34yz00	OTHER SPECIFIED OPERATIONS ON CORONARY ARTERY
me_3159	re_G3y..00	OTHER SPECIFIED OTHER BYPASS OF CORONARY ARTERY
me_95382	re_792y.00	OTHER SPECIFIED OTHER OPEN OPERATION ON CORONARY ARTERY
me_69247	re_792Dy00	OTHER SPECIFIED REPAIR OF CORONARY ARTERY
me_93828	re_7927y00	OTHER SPECIFIED REPLACEMENT OF CORONARY ARTERY
me_97953	re_792By00	OTHER SPECIFIED REVISION OF BYPASS FOR CORONARY ARTERY
me_31679	re_792Cy00	OTHER THERAPEUTIC TRANSLUMINAL OP ON CORONARY ARTERY NOS
me_6182	re_7924y00	OTHER THERAPEUTIC TRANSLUMINAL OP ON CORONARY ARTERY OS
me_24888	re_7929z00	OTHER THERAPEUTIC TRANSLUMINAL OPERATIONS ON CORONARY ARTERY
me_87849	re_7929y00	PERC TRAN BALL ANGIO INS 3 OR MORE DRUG ELUT STENTS COR ART
me_60067	re_7929.00	PERC TRANSLUM BALL ANGIO INSERT 1-2 DRUG ELUT STENTS COR ART
me_85947	re_793G100	PERC TRANSLUM BALLOON ANGIOPLASTY INSERT 1-2 STENTS COR ART
me_61208	re_793G000	PERC TRANSLUM BALLOON ANGIOPLASTY STENTING CORONARY ART NOS
me_43939	re_793G200	PERC TRANSLUMIN BALLOON ANGIOPLASTY STENTING CORONARY ARTERY
me_42462	re_793Gz00	PERCUT TRANSLUM BALLOON ANGIOPLASTY BYPASS GRAFT CORONARY A
me_33735	re_793G.00	PERCUT TRANSLUM BALLOON ANGIOPLASTY MULT CORONARY ARTERIES
me_40996	re_7928200	PERCUT TRANSLUM CORONARY THROMBOLYTIC THERAPY-STREPTOKINASE
me_86071	re_7928100	PERCUT TRANSLUM CUTTING BALLOON ANGIOPLASTY CORONARY ARTERY
me_66583	re_7929111	PERCUT TRANSLUM INJECT THERAP SUBST TO CORONARY ARTERY NEC
me_18670	re_7928300	PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY
me_33650	re_7929200	PERCUT TRANSLUMINAL CORONARY THROMBOLYSIS WITH STREPTOKINASE
me_5703	re_7928000	PERCUTANEOUS BALLOON CORONARY ANGIOPLASTY
me_92927	re_7929100	PERCUTANEOUS COR BALLOON ANGIOP 3 MORE STENTS COR ART NEC
me_66921	re_7928.11	PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY OF VASCULAR GRAFT
me_93618	re_793G300	PERCUTANEOUS TRANSLUMINAL ATHERECTOMY OF CORONARY ARTERY
me_93706	re_7A6H400	PERCUTANEOUS TRANSLUMINAL BALLOON DILATION CARDIAC CONDUIT
me_22828	re_7929600	PERCUTANEOUS TRANSLUMINAL LASER CORONARY ANGIOPLASTY
me_20903	re_793H000	PEROPERATIVE ANGIOPLASTY
me_17464	re_7929000	PERSONAL HISTORY OF MYOCARDIAL INFARCTION
me_9555	re_7A6G100	POST INFARCT ANGINA

me_35119	re_G32..12	POST INFARCTION PERICARDITIS
me_23892	re_G33z500	POSTERIOR MYOCARDIAL INFARCTION NOS
me_23579	re_G501.00	POSTMYOCARDIAL INFARCTION SYNDROME
me_32272	re_G304.00	POSTOPERATIVE MYOCARDIAL INFARCTION
me_68748	re_G310.00	POSTOPERATIVE MYOCARDIAL INFARCTION, UNSPECIFIED
me_41835	re_G38..00	POSTOPERATIVE SUBENDOCARDIAL MYOCARDIAL INFARCTION
me_46112	re_G38z.00	POSTOPERATIVE TRANSMURAL MYOCARDIAL INFARCTION ANTERIOR WALL
me_46276	re_G384.00	POSTOPERATIVE TRANSMURAL MYOCARDIAL INFARCTION INFERIOR WALL
me_106812	re_G380.00	POSTOPERATIVE TRANSMURAL MYOCARDIAL INFARCTION UNSPEC SITE
me_36523	re_G381.00	PREINFARCTION SYNDROME
me_54251	re_G383.00	PREINFARCTION SYNDROME NOS
me_12986	re_G311.00	PRINZMETAL'S ANGINA
me_36011	re_G311z00	PROSTHETIC BYPASS OF CORONARY ARTERY
me_64923	re_G331.00	PROSTHETIC GRAFT PATCH ANGIOPLASTY
me_19402	re_7923.11	PROSTHETIC REPLACEMENT OF CORONARY ARTERY
me_19193	re_7A6H300	PROSTHETIC REPLACEMENT OF CORONARY ARTERY NOS
me_67761	re_7923.00	PROSTHETIC REPLACEMENT OF FOUR OR MORE CORONARY ARTERIES
me_92419	re_7923z00	PROSTHETIC REPLACEMENT OF ONE CORONARY ARTERY
me_66236	re_7923300	PROSTHETIC REPLACEMENT OF THREE CORONARY ARTERIES
me_66664	re_7923000	PROSTHETIC REPLACEMENT OF TWO CORONARY ARTERIES
me_34328	re_7923200	REFRACTORY ANGINA
me_33620	re_7923100	REPAIR OF CORONARY ARTERY NEC
me_44585	re_G311300	REPAIR OF CORONARY ARTERY NOS
me_55092	re_792B.00	REPLACEMENT OF CORONARY ARTERIES USING MULTIPLE METHODS
me_70755	re_792Bz00	REPLACEMENT OF CORONARY ARTERY NOS
me_33461	re_792C000	REVISION OF BYPASS FOR CORONARY ARTERY
me_57634	re_792Cz00	REVISION OF BYPASS FOR CORONARY ARTERY NOS
me_101569	re_7924.00	REVISION OF BYPASS FOR FOUR OR MORE CORONARY ARTERIES
me_52938	re_7924z00	REVISION OF BYPASS FOR ONE CORONARY ARTERY
me_31540	re_7924300	REVISION OF BYPASS FOR THREE CORONARY ARTERIES
me_67554	re_7924000	REVISION OF BYPASS FOR TWO CORONARY ARTERIES
me_63153	re_7924200	REVISION OF IMPLANTATION OF THORACIC ARTERY INTO HEART
me_92233	re_7924100	RIMA SEQUENTIAL ANASTOMOSIS
me_68123	re_7924500	RIMA SINGLE ANASTOMOSIS
me_38813	re_7925012	ROTARY BLADE ANGIOPLASTY
me_19046	re_7925312	ROTARY BLADE CORONARY ANGIOPLASTY
me_59189	re_7A54500	RUPTUR CARDIAC WALL W'OUT HAEMOPERICARD/CUR COMP FOL AC MI
me_59940	re_7929300	RUPTUR CHORDAE TENDINAE/CURR COMP FOL ACUTE MYOCARD INFARCT
me_69474	re_G363.00	RUPTURE PAPILLARY MUSCLE/CURR COMP FOL ACUTE MYOCARD INFARCT
me_8312	re_G364.00	SAPHENOUS VEIN GRAFT BYPASS OF CORONARY ARTERY
me_51515	re_G365.00	SAPHENOUS VEIN GRAFT REPLACEMENT CORONARY ARTERY NOS

me_18249	re_7920.11	SAPHENOUS VEIN GRAFT REPLACEMENT OF CORONARY ARTERY
me_7137	re_7920z00	SAPHENOUS VEIN GRAFT REPLACEMENT OF CORONARY ARTERY OS
me_11610	re_7920.00	SAPHENOUS VEIN GRAFT REPLACEMENT OF FOUR+ CORONARY ARTERIES
me_8679	re_7920y00	SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY
me_7442	re_7920300	SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES
me_7634	re_7920000	SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES
me_17689	re_7920200	SILENT MYOCARDIAL INFARCTION
me_29421	re_7920100	SILENT MYOCARDIAL ISCHAEMIA
me_44723	re_G30..17	SINGLE ANAST MAMMARY ART TO LEFT ANT DESCEND CORONARY ART
me_51507	re_G344.00	SINGLE ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC
me_67591	re_7925200	SINGLE ANASTOMOSIS OF THORACIC ARTERY TO CORONARY ARTERY NEC
me_3999	re_7925300	SINGLE CORONARY VESSEL DISEASE
me_68139	re_7926200	SINGLE IMPLANTATION OF MAMMARY ARTERY INTO CORONARY ARTERY
me_60753	re_G340000	SINGLE IMPLANTATION THORACIC ARTERY INTO CORONARY ARTERY NEC
me_12804	re_7925400	STABLE ANGINA
me_66388	re_7926300	STATUS ANGINOSUS
me_54535	re_G33z700	STENOCARDIA
me_39693	re_G33z000	SUBENDOCARDIAL ISCHAEMIA
me_18842	re_G33z100	SUBSEQUENT MYOCARDIAL INFARCTION
me_45809	re_G31y200	SUBSEQUENT MYOCARDIAL INFARCTION OF ANTERIOR WALL
me_38609	re_G35..00	SUBSEQUENT MYOCARDIAL INFARCTION OF INFERIOR WALL
me_72562	re_G350.00	SUBSEQUENT MYOCARDIAL INFARCTION OF OTHER SITES
me_46166	re_G351.00	SUBSEQUENT MYOCARDIAL INFARCTION OF UNSPECIFIED SITE
me_7696	re_G353.00	SYNCOPE ANGINOSA
me_13571	re_G35X.00	THROMBOSIS - CORONARY
me_29553	re_G33z200	THROMBOSIS ATRIUM,AURIC APPEND&VENT/CURR COMP FOLL ACUTE MI
me_21844	re_G30..16	TRANSIENT MYOCARDIAL ISCHAEMIA
me_2901	re_G366.00	TRANSLUMINAL BALLOON ANGIOPLASTY OF CORONARY ARTERY
me_732	re_G31y300	TRANSLUMINAL BALLOON ANGIOPLASTY OF CORONARY ARTERY NOS
me_41547	re_7928.00	TRANSLUMINAL BALLOON ANGIOPLASTY OF CORONARY ARTERY OS
me_48206	re_7928z00	TRANSPOSITION OF CORONARY ARTERY NEC
me_1655	re_7928y00	TRIPLE VESSEL DISEASE OF THE HEART
me_63467	re_7927300	TRUE POSTERIOR MYOCARDIAL INFARCTION
me_1431	re_G340.11	UNSTABLE ANGINA
me_7347	re_G306.00	UNSTABLE ANGINA
me_11048	re_G311.13	VARIANT ANGINA PECTORIS
me_37657	re_G311100	VENTRIC SEPTAL DEFECT/CURR COMP FOL ACUT MYOCARDAL INFARCTN
me_2155	re_G331.11	VENTRICULAR CARDIAC ANEURYSM
me_18118	re_G362.00	WORSENING ANGINA

me_18913	re_G341000	[V]PRESENCE OF AORTOCORONARY BYPASS GRAFT
me_18643	re_G311400	[V]PRESENCE OF CORONARY ANGIOPLASTY IMPLANT AND GRAFT
me_5030	re_ZV45700	[V]PRESENCE OF CORONARY ARTERY BYPASS GRAFT
me_5674	re_ZV45800	[V]PRESENCE OF CORONARY ARTERY BYPASS GRAFT - CABG
me_6980	re_ZV45K00	[V]STATUS FOLLOWING CORONARY ANGIOPLASTY NOS
me_96838	re_ZV45K11	[X]ACUTE TRANSMURAL MYOCARDIAL INFARCTION OF UNSPECIF SITE
me_39546	re_ZV45L00	[X]OTHER FORMS OF ANGINA PECTORIS
me_109035	re_Gyu3400	[X]SUBSEQUENT MYOCARDIAL INFARCTION OF OTHER SITES
me_99991	re_Gyu3000	[X]SUBSEQUENT MYOCARDIAL INFARCTION OF UNSPECIFIED SITE
	re_Gyu3500	
	re_Gyu3600	
Deep Vein Thrombosis		
me_42506	re_G801C00	DEEP VEIN THROMBOSIS OF LEG RELATED TO AIR TRAVEL
me_48920	re_G801E00	DEEP VEIN THROMBOSIS OF LEG RELATED TO INTRAVENOUS DRUG USE
me_22038	re_G801D00	DEEP VEIN THROMBOSIS OF LOWER LIMB
me_98526	re_G801F00	DEEP VEIN THROMBOSIS OF PERONEAL VEIN
	re_G801D99	DEEP VENOUS THROMBOSIS - LEG
me_104342	re_G801G00	RECURRENT DEEP VEIN THROMBOSIS
me_96209	re_G401100	RECURRENT PULMONARY EMBOLISM

Common Infections

medcode	reado_code	description
cough/cold		
me_3260	re_H00..00	ACUTE NASOPHARYNGITIS
me_1025	re_1719.11	BRONCHIAL COUGH
me_1273	re_171..11	C/O - COUGH
me_2476	re_H07..00	CHEST COLD
me_292	re_1719.00	CHESTY COUGH
me_368	re_H00..11	COMMON COLD
me_1246	re_H00..12	CORYZA - ACUTE
me_92	re_171..00	COUGH
me_7707	re_171Z.00	COUGH SYMPTOM NOS
me_18907	re_171F.00	COUGH WITH FEVER
me_3645	re_1716.11	COUGHING UP PHLEGM
me_4931	re_1712.00	DRY COUGH
me_6620	re_H00..13	FEBRILE COLD
me_2157	re_H27z.11	FLU LIKE ILLNESS
me_5947	re_H27z.12	INFLUENZA LIKE ILLNESS
me_8980	re_16L..00	INFLUENZA-LIKE SYMPTOMS
me_896	re_H00..14	NASAL CATARRH - ACUTE
me_3628	re_171B.00	PERSISTENT COUGH

me_7706	re_1713.00	PRODUCTIVE COUGH -CLEAR SPUTUM
me_7773	re_1714.00	PRODUCTIVE COUGH -GREEN SPUTUM
me_1234	re_1716.00	PRODUCTIVE COUGH NOS
me_7708	re_1715.00	PRODUCTIVE COUGH-YELLOW SPUTUM
me_9093	re_H00..15	PYREXIAL COLD
me_3821	re_H00..16	RHINITIS - ACUTE
	re_A33..00	WHOOPING COUGH
	re_R062.00	[D]COUGH
lower respiratory tract infection		
me_24800	re_H060x00	ACUTE BACTERIAL BRONCHITIS UNSPECIFIED
me_1019	re_H061.00	ACUTE BRONCHIOLITIS
me_17917	re_H061z00	ACUTE BRONCHIOLITIS NOS
me_17185	re_H061200	ACUTE BRONCHIOLITIS WITH BRONCHOSPASM
me_312	re_H060.00	ACUTE BRONCHITIS
me_29669	re_H06..00	ACUTE BRONCHITIS AND BRONCHIOLITIS
me_31886	re_H060A00	ACUTE BRONCHITIS DUE TO MYCOPLASMA PNEUMONIAE
me_20198	re_H060z00	ACUTE BRONCHITIS NOS
me_41137	re_H06z.00	ACUTE BRONCHITIS OR BRONCHIOLITIS NOS
me_54533	re_H061000	ACUTE CAPILLARY BRONCHIOLITIS
me_21145	re_H060400	ACUTE CROUPOUS BRONCHITIS
me_19207	re_H510300	ACUTE DRY PLEURISY
me_69192	re_H061300	ACUTE EXUDATIVE BRONCHIOLITIS
me_50396	re_H060000	ACUTE FIBRINOUS BRONCHITIS
me_21492	re_H060800	ACUTE HAEMOPHILUS INFLUENZAE BRONCHITIS
me_37447	re_H062.00	ACUTE LOWER RESPIRATORY TRACT INFECTION
me_6124	re_H06z112	ACUTE LOWER RESPIRATORY TRACT INFECTION
me_9043	re_H060600	ACUTE PNEUMOCOCCAL BRONCHITIS
me_11072	re_H060300	ACUTE PURULENT BRONCHITIS
me_43362	re_H060700	ACUTE STREPTOCOCCAL BRONCHITIS
me_11101	re_H060500	ACUTE TRACHEOBRONCHITIS
me_5978	re_H060.11	ACUTE WHEEZY BRONCHITIS
me_2195	re_H34..00	BRONCHIECTASIS
me_32679	re_H34z.00	BRONCHIECTASIS NOS
me_26125	re_H312300	BRONCHIOLITIS OBLITERANS
me_3480	re_H30z.00	BRONCHITIS NOS
me_148	re_H30..00	BRONCHITIS UNSPECIFIED
me_68	re_H06z011	CHEST INFECTION
me_17359	re_H30..11	CHEST INFECTION - UNSPECIFIED BRONCHITIS
me_2581	re_H06z000	CHEST INFECTION NOS
me_24316	re_H24..11	CHEST INFECTION WITH INFECTIOUS DISEASE EC
me_14798	re_H312100	EMPHYSEMATOUS BRONCHITIS
me_2375	re_H50..00	EMPYEMA
me_34651	re_H500100	EMPYEMA WITH BRONCHOPLEURAL FISTULA
me_106650	re_H583200	EOSINOPHILIC BRONCHITIS
me_1934	re_H301.00	LARYNGOTRACHEOBRONCHITIS

me_3358	re_H06z100	LOWER RESP TRACT INFECTION
me_44425	re_H501200	PLEURAL EMPYEMA
me_978	re_H51..00	PLEURISY
me_32818	re_H510900	PNEUMOCOCCAL PLEURISY
me_41491	re_H341.00	POST-INFECTIVE BRONCHIECTASIS
me_49452	re_H501400	PURULENT PLEURISY
me_20364	re_H340.00	RECURRENT BRONCHIECTASIS
me_4899	re_H06z200	RECURRENT CHEST INFECTION
me_7092	re_H30..12	RECURRENT WHEEZY BRONCHITIS
me_293	re_H06z111	RESPIRATORY TRACT INFECTION
me_3163	re_H300.00	TRACHEOBRONCHITIS NOS
me_152	re_H302.00	WHEEZY BRONCHITIS
me_66397	re_Hyu1.00	[X]OTHER ACUTE LOWER RESPIRATORY INFECTIONS
otitis externa		
me_16969	re_F506.00	ABSCESS OF EXTERNAL EAR
me_20144	re_F501111	ABSCESS, EXTERNAL EAR
me_15107	re_F501200	ACUTE INFECTION OF PINNA
me_14907	re_F501100	ACUTE INFECTIVE OTITIS EXTERNA
me_43616	re_F500100	ACUTE PERICHONDRITIS OF PINNA
me_22384	re_F501300	ACUTE SWIMMERS' EAR
me_8852	re_F501112	CELLULITIS, EXTERNAL EAR
me_16847	re_F500211	CHONDRODERMATITIS NODULARIS HELICIS
me_7548	re_F500300	CHONDRODERMATITIS NODULARIS HELICIS
me_8700	re_F501F00	CHRONIC INFECTIVE OTITIS EXTERNA NOS
me_38719	re_F500200	CHRONIC PINNA PERICHONDRITIS
me_1135	re_F587.11	EAR PAIN
me_27616	re_F501411	ERYSIPELAS - OTITIS EXTERNA
me_26065	re_F501G00	HAEMORRHAGIC OTITIS EXTERNA
me_17353	re_F501711	IMPETIGO - OTITIS EXTERNA
me_2138	re_F501.00	INFECTIVE OTITIS EXTERNA
me_68242	re_F501400	INFECTIVE OTITIS EXTERNA DUE TO ERYSIPELAS
me_16249	re_F501700	INFECTIVE OTITIS EXTERNA DUE TO IMPETIGO
me_41120	re_F501z00	INFECTIVE OTITIS EXTERNA NOS
me_5537	re_F502z11	INFLAMMATION EAR EXTERNAL
me_731	re_F587.00	OTALGIA
me_44481	re_F587z00	OTALGIA NOS
me_36760	re_F501900	OTHER ACUTE EXTERNAL EAR INFECTIONS
me_27669	re_F501E00	OTHER CHRONIC INFECTIVE OTITIS EXTERNA
me_3350	re_F502.00	OTHER OTITIS EXTERNA
me_41806	re_F501y00	OTHER SPECIFIED INFECTIVE OTITIS EXTERNA
me_630	re_F502z00	OTITIS EXTERNA NOS
me_1102	re_F500.00	PERICHONDRITIS OF PINNA
me_14863	re_F500z00	PERICHONDRITIS OF PINNA NOS
me_1242	re_F501000	UNSPECIFIED INFECTIVE OTITIS EXTERNA
me_25171	re_F587000	UNSPECIFIED OTALGIA
me_41506	re_F500000	UNSPECIFIED PERICHONDRITIS OF PINNA

otitis media		
me_1134	re_F528.00	ACUTE BILATERAL OTITIS MEDIA
me_3694	re_F526.00	ACUTE LEFT OTITIS MEDIA
me_21012	re_F510200	ACUTE MUCOID OTITIS MEDIA
me_5887	re_F510.00	ACUTE NON SUPPURATIVE OTITIS MEDIA
me_20374	re_F510z00	ACUTE NONSUPPURATIVE OTITIS MEDIA NOS
me_18371	re_F510000	ACUTE OTITIS MEDIA WITH EFFUSION
me_4348	re_F527.00	ACUTE RIGHT OTITIS MEDIA
me_15973	re_F510300	ACUTE SANGUINOUS OTITIS MEDIA
me_5148	re_F510011	ACUTE SECRETORY OTITIS MEDIA
me_7730	re_F510100	ACUTE SEROUS OTITIS MEDIA
me_2137	re_F520.00	ACUTE SUPPURATIVE OTITIS MEDIA
me_61497	re_F520300	ACUTE SUPPURATIVE OTITIS MEDIA DUE TO DISEASE E
me_20372	re_F520z00	ACUTE SUPPURATIVE OTITIS MEDIA NOS
me_10781	re_F520000	ACUTE SUPPURATIVE OTITIS MEDIA TYMPANIC MEMBRAN
me_20669	re_F520100	ACUTE SUPPURATIVE OTITIS MEDIA TYMPANIC MEMBRAN
me_46709	re_SN30.11	AERO-OTITIS MEDIA
me_20871	re_F524000	BILATERAL SUPPURATIVE OTITIS MEDIA
me_7479	re_F515.11	CATARRH - EUSTACHIAN
me_5390	re_F514200	CATARRHAL OTITIS MEDIA NOS
me_20578	re_F512z00	CHRONIC MUCOID OTITIS MEDIA NOS
me_2686	re_F512.00	CHRONIC OTITIS MEDIA WITH EFFUSION, MUCOID
me_34348	re_F513.00	CHRONIC OTITIS MEDIA WITH EFFUSION, OTHER
me_25188	re_F513100	CHRONIC OTITIS MEDIA WITH EFFUSION, PURULENT
me_6559	re_F511.00	CHRONIC OTITIS MEDIA WITH EFFUSION, SEROUS
me_1184	re_F512.12	CHRONIC SECRETORY OTITIS MEDIA, MUCOID
me_9993	re_F513111	CHRONIC SECRETORY OTITIS MEDIA, PURULENT
me_24742	re_F511.11	CHRONIC SECRETORY OTITIS MEDIA, SEROUS
me_33661	re_F511z00	CHRONIC SEROUS OTITIS MEDIA NOS
me_1376	re_F523.00	CHRONIC SUPPURATIVE OTITIS MEDIA NOS
me_24590	re_F522.00	CHRONIC SUPPURATIVE OTITIS MEDIA, ATTICOANTRAL
me_17866	re_F521.00	CHRONIC SUPPURATIVE OTITIS MEDIA, TUBOTYMPANIC
me_6415	re_F586011	DISCHARGING EAR NOS
me_16121	re_F515.00	EUSTACHIAN TUBE SALPINGITIS
me_354	re_F512.11	GLUE EAR
me_5539	re_F512000	GLUE EAR, UNSPECIFIED
me_1513	re_F52z.11	INFECTION EAR
me_21749	re_F514300	MUCOID OTITIS MEDIA NOS
me_5577	re_F51..00	NONSUPPURATIVE OTITIS MEDIA + EUSTACHIAN TUBE D
me_21725	re_F514z00	NONSUPPURATIVE OTITIS MEDIA NOS
me_18363	re_2D95.00	O/E - TYMPANIC MEMBRANE RED
me_267	re_F52z.00	OTITIS MEDIA NOS
me_6958	re_F586200	OTORRHAGIA
me_638	re_F586.00	OTORRHOEA
me_15510	re_F586z00	OTORRHOEA NOS

me_5903	re_A552.00	POSTMEASLES OTITIS MEDIA
me_15568	re_F524.00	PURULENT OTITIS MEDIA NOS
me_9973	re_F525.00	RECURRENT ACUTE OTITIS MEDIA
me_5102	re_F514100	SEROUS OTITIS MEDIA NOS
me_1474	re_F52..00	SUPPURATIVE AND UNSPECIFIED OTITIS MEDIA
me_17772	re_F514.00	UNSPECIFIED NONSUPPURATIVE OTITIS MEDIA
me_16244	re_F586000	UNSPECIFIED OTORRHOEA
sinusitis		
me_15724	re_H012.00	ACUTE ETHMOIDAL SINUSITIS
me_8213	re_H011.00	ACUTE FRONTAL SINUSITIS
me_7021	re_H010.00	ACUTE MAXILLARY SINUSITIS
me_94218	re_H014.00	ACUTE RHINOSINUSITIS
me_980	re_H01..00	ACUTE SINUSITIS
me_33664	re_H01z.00	ACUTE SINUSITIS NOS
me_38816	re_H013.00	ACUTE SPHENOIDAL SINUSITIS
me_33437	re_H130.11	ANTRITIS - CHRONIC
me_1674	re_H132.00	CHRONIC ETHMOIDAL SINUSITIS
me_15163	re_H131.00	CHRONIC FRONTAL SINUSITIS
me_4433	re_H130.00	CHRONIC MAXILLARY SINUSITIS
me_39501	re_H13y000	CHRONIC PANSINUSITIS
me_10546	re_H13..11	CHRONIC RHINOSINUSITIS
me_2257	re_H13..00	CHRONIC SINUSITIS
me_5437	re_H13z.00	CHRONIC SINUSITIS NOS
me_29429	re_H134.00	FISTULA OF NASAL SINUS
me_2984	re_H131.11	FRONTAL SINUSITIS
me_3624	re_H130.12	MAXILLARY SINUSITIS
me_29696	re_H01y.00	OTHER ACUTE SINUSITIS
me_60733	re_H01yz00	OTHER ACUTE SINUSITIS NOS
me_49548	re_H13y.00	OTHER CHRONIC SINUSITIS
me_54375	re_H13yz00	OTHER CHRONIC SINUSITIS NOS
me_2233	re_H13y100	PANSINUSITIS
me_17173	re_H135.00	RECURRENT SINUSITIS
me_243	re_H01..11	SINUSITIS
me_97330	re_Hyu0000	[X]OTHER ACUTE SINUSITIS
throat		
me_17899	re_H023.00	ACUTE BACTERIAL PHARYNGITIS
me_53395	re_H023z00	ACUTE BACTERIAL PHARYNGITIS NOS
me_10156	re_H035.00	ACUTE BACTERIAL TONSILLITIS
me_15970	re_H035z00	ACUTE BACTERIAL TONSILLITIS NOS
me_37409	re_H033.00	ACUTE CATARRHAL TONSILLITIS
me_12010	re_H030.00	ACUTE ERYTHEMATOUS TONSILLITIS
me_4061	re_H031.00	ACUTE FOLLICULAR TONSILLITIS
me_893	re_H02..00	ACUTE PHARYNGITIS
me_407	re_H02z.00	ACUTE PHARYNGITIS NOS
me_24708	re_H021.00	ACUTE PHLEGMONOUS PHARYNGITIS
me_64973	re_H035100	ACUTE STAPHYLOCOCCAL TONSILLITIS

me_138	re_H03..00	ACUTE TONSILLITIS
me_20104	re_H03z.00	ACUTE TONSILLITIS NOS
me_21486	re_H022.00	ACUTE ULCERATIVE PHARYNGITIS
me_8452	re_H032.00	ACUTE ULCERATIVE TONSILLITIS
me_36462	re_H14y500	CASEOUS TONSILLITIS
me_35249	re_H14y600	LINGULAR TONSILLITIS
me_4748	re_J083.00	ORAL CELLULITIS AND ABSCESS
me_3605	re_H15..00	PERITONSILLAR ABSCESS - QUINSY
me_911	re_H15..11	QUINSY
me_1747	re_H037.00	RECURRENT ACUTE TONSILLITIS
me_3218	re_A341.12	SCARLATINA
me_456	re_A341.11	SCARLET FEVER
me_8210	re_A341.00	SCARLET FEVER - SCARLATINA
me_6014	re_H02..11	SORE THROAT NOS
me_5755	re_1C9..00	SORE THROAT SYMPTOM
me_15287	re_1C9Z.00	SORE THROAT SYMPTOM NOS
me_24176	re_A340000	STREPTOCOCCAL ANGINA
me_4902	re_A340200	STREPTOCOCCAL PHARYNGITIS
me_1765	re_A340.00	STREPTOCOCCAL SORE THROAT
me_54777	re_A34..00	STREPTOCOCCAL SORE THROAT AND SCARLATINA
me_16217	re_A340z00	STREPTOCOCCAL SORE THROAT NOS
me_16184	re_A34z.00	STREPTOCOCCAL SORE THROAT WITH SCARLATINA NOS
me_8496	re_A340300	STREPTOCOCCAL TONSILLITIS
me_310	re_H02..13	THROAT INFECTION - PHARYNGITIS
me_11499	re_H03..11	THROAT INFECTION - TONSILLITIS
me_404	re_1C9..11	THROAT SORENESS
me_2125	re_H03..12	TONSILLITIS
me_16197	re_AA1..11	TRENCH MOUTH
me_8480	re_J083600	UVULITIS
me_5096	re_AA1..00	VINCENT'S ANGINA
me_72176	re_AA1z.00	VINCENT'S ANGINA NOS
me_20896	re_AA11.00	VINCENT'S GINGIVITIS
me_16067	re_AA1z.11	VINCENT'S LARYNGITIS
me_31536	re_AA12.00	VINCENT'S PHARYNGITIS
me_35750	re_AA10.00	VINCENT'S STOMATITIS
me_16954	re_AA1z.12	VINCENT'S TONSILLITIS
me_6466	re_H02..12	VIRAL SORE THROAT NOS
me_15039	re_R041.00	[D]THROAT PAIN
me_93964	re_Hyu0100	[X]ACUTE PHARYNGITIS DUE TO OTHER SPECIFIED O
me_73118	re_Hyu0200	[X]ACUTE TONSILLITIS DUE TO OTHER SPECIFIED O
upper respiratory tract infection		
me_52756	re_H040x00	ACUTE BACTERIAL LARYNGITIS UNSPECIFIED
me_10765	re_H040200	ACUTE CATARRHAL LARYNGITIS
me_10641	re_H043.00	ACUTE EPIGLOTTITIS (NON STREP)
me_892	re_H043z00	ACUTE EPIGLOTTITIS NOS

me_65650	re_H043000	ACUTE EPIGLOTTITIS WITHOUT OBSTRUCTION
me_142	re_H040.00	ACUTE LARYNGITIS
me_41324	re_H04..00	ACUTE LARYNGITIS AND TRACHEITIS
me_16120	re_H04z.00	ACUTE LARYNGITIS AND TRACHEITIS NOS
me_22720	re_H040z00	ACUTE LARYNGITIS NOS
me_18908	re_H050.00	ACUTE LARYNGOPHARYNGITIS
me_10087	re_H042.00	ACUTE LARYNGOTRACHEITIS
me_24471	re_H042z00	ACUTE LARYNGOTRACHEITIS NOS
me_69898	re_H042100	ACUTE LARYNGOTRACHEITIS WITH OBSTRUCTION
me_25259	re_H042000	ACUTE LARYNGOTRACHEITIS WITHOUT OBSTRUCTION
me_38128	re_H043200	ACUTE OBSTRUCTIVE LARYNGITIS
me_26038	re_H040000	ACUTE OEDEMATOUS LARYNGITIS
me_31501	re_H040300	ACUTE PHLEGMONOUS LARYNGITIS
me_21113	re_H0z..00	ACUTE RESPIRATORY INFECTION NOS
me_8025	re_H0...00	ACUTE RESPIRATORY INFECTIONS
me_51562	re_H040600	ACUTE SUPPURATIVE LARYNGITIS
me_1257	re_H041.00	ACUTE TRACHEITIS
me_16313	re_H041z00	ACUTE TRACHEITIS NOS
me_68867	re_H041100	ACUTE TRACHEITIS WITH OBSTRUCTION
me_12476	re_H041000	ACUTE TRACHEITIS WITHOUT OBSTRUCTION
me_62885	re_H040100	ACUTE ULCERATIVE LARYNGITIS
me_6294	re_H051.00	ACUTE UPPER RESPIRATORY TRACT INFECTION
me_17513	re_H160100	CHRONIC CATARRHAL LARYNGITIS
me_1285	re_H042.11	LARYNGOTRACHEITIS
me_26010	re_H05..00	OTHER ACUTE UPPER RESPIRATORY INFECTIONS
me_23640	re_H0y..00	OTHER SPECIFIED ACUTE RESPIRATORY INFECTIONS
me_15628	re_H05y.00	OTHER UPPER RESPIRATORY INFECTIONS OF MULTIPL
me_4718	re_H055.00	PHARYNGOLARYNGITIS
me_21415	re_H052.00	PHARYNGOTRACHEITIS
me_4221	re_H054.00	RECURRENT UPPER RESPIRATORY TRACT INFECTION
me_7074	re_H5yy.11	RESPIRATORY INFECTION NOS
me_16718	re_A340100	STREPTOCOCCAL LARYNGITIS
me_10093	re_H053.00	TRACHEOPHARYNGITIS
me_76	re_H05z.00	UPPER RESPIRATORY INFECTION NOS
me_2637	re_H05z.11	UPPER RESPIRATORY TRACT INFECTION NOS
me_53055	re_Hyu0.00	[X]ACUTE UPPER RESPIRATORY INFECTIONS
urinary tract infection		
me_15074	re_K150.00	ACUTE CYSTITIS
me_10233	re_K190011	ASYMPTOMATIC BACTERIURIA
me_4993	re_K190000	BACTERIURIA, SITE NOT SPECIFIED
me_107568	re_SP07Q00	CATHETER-ASSOCIATED URINARY TRACT INFECTION
me_107843	re_SP07Q11	CAUTI - CATHETER-ASSOCIATED URINARY TRACT INF
me_389	re_K15..00	CYSTITIS
me_12484	re_K15z.00	CYSTITIS NOS
me_2602	re_L166.11	CYSTITIS OF PREGNANCY
me_16017	re_L166100	GENITOURINARY TRACT INFECTION IN PREGNANCY -

me_15634	re_L166z00	GENITOURINARY TRACT INFECTION IN PREGNANCY NO
me_27451	re_L166000	GENITOURINARY TRACT INFECTION IN PREGNANCY UN
me_67975	re_L166.00	GENITOURINARY TRACT INFECTIONS IN PREGNANCY
me_3029	re_L166500	INFECTIONS OF KIDNEY IN PREGNANCY
me_12570	re_K190200	POST OPERATIVE URINARY TRACT INFECTION
me_1353	re_K155.00	RECURRENT CYSTITIS
me_10515	re_K190.11	RECURRENT URINARY TRACT INFECTION
me_1572	re_K190300	RECURRENT URINARY TRACT INFECTION
me_9378	re_1AG..00	RECURRENT URINARY TRACT INFECTIONS
me_2985	re_K190311	RECURRENT UTI
me_7579	re_1J4..00	SUSPECTED UTI
me_97002	re_K190500	URINARY TRACT INFECTION
me_6649	re_L166800	URINARY TRACT INFECTION COMPLICATING PREGNANC
me_5721	re_L166600	URINARY TRACT INFECTION FOLLOWING DELIVERY
me_1289	re_K190.00	URINARY TRACT INFECTION, SITE NOT SPECIFIED
me_150	re_K190z00	URINARY TRACT INFECTION, SITE NOT SPECIFIED N
me_14644	re_L166z11	UTI - URINARY TRACT INFECTION IN PREGNANCY
renal infection		
me_14828	re_K101200	ACUTE PYELITIS
me_2546	re_K101.00	ACUTE PYELONEPHRITIS
me_38698	re_K101z00	ACUTE PYELONEPHRITIS NOS
me_2939	re_K100600	CALCULOUS PYELONEPHRITIS
me_4255	re_K10z.00	INFECTION OF KIDNEY NOS
me_3610	re_K102100	PERINEPHRIC ABSCESS
me_1106	re_K10y100	PYELITIS UNSPECIFIED
me_53944	re_K10y.00	PYELONEPHRITIS AND PYONEPHROSIS UNSPECIFIED
me_1899	re_K10y000	PYELONEPHRITIS UNSPECIFIED
me_15357	re_K102000	RENAL ABSCESS
me_49212	re_K102200	RENAL CARBUNCLE
me_59121	re_K10yz00	UNSPECIFIED PYELONEPHRITIS NOS
asthma/copd		
me_185	re_H333.00	ACUTE EXACERBATION OF ASTHMA
me_1446	re_H312200	ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWA
me_2290	re_H330.11	ALLERGIC ASTHMA
me_21232	re_H33zz12	ALLERGIC ASTHMA NEC
me_18207	re_H33zz13	ALLERGIC BRONCHITIS NEC
me_78	re_H33..00	ASTHMA
me_232	re_H33z100	ASTHMA ATTACK
me_8335	re_H33z111	ASTHMA ATTACK NOS
me_16070	re_H33zz00	ASTHMA NOS
me_4442	re_H33z.00	ASTHMA UNSPECIFIED
me_40823	re_H334.00	BRITTLE ASTHMA
me_1555	re_H33..11	BRONCHIAL ASTHMA
me_1208	re_H330.12	CHILDHOOD ASTHMA
me_7884	re_H3y1.00	CHRON OBSTRUCT PULMONARY DIS WTH ACUTE EXACERBA

me_106805	re_H335.00	CHRONIC ASTHMA WITH FIXED AIRFLOW OBSTRUCTION
me_21061	re_H3y0.00	CHRONIC OBSTRUCT PULMONARY DIS WITH ACUTE LOWER
me_998	re_H3...11	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE
me_5710	re_H3z..00	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE NOS
me_1001	re_H3...00	CHRONIC OBSTRUCTIVE PULMONARY DISEASE
me_37247	re_H3z..11	CHRONIC OBSTRUCTIVE PULMONARY DISEASE NOS
me_4606	re_173A.00	EXERCISE INDUCED ASTHMA
me_5867	re_H33zz11	EXERCISE INDUCED ASTHMA
me_7146	re_H330.00	EXTRINSIC (ATOPIC) ASTHMA
me_45782	re_H330z00	EXTRINSIC ASTHMA NOS
me_6707	re_H330111	EXTRINSIC ASTHMA WITH ASTHMA ATTACK
me_27926	re_H330100	EXTRINSIC ASTHMA WITH STATUS ASTHMATICUS
me_14777	re_H330000	EXTRINSIC ASTHMA WITHOUT STATUS ASTHMATICUS
me_15248	re_H330.13	HAY FEVER WITH ASTHMA
me_5627	re_H330011	HAY FEVER WITH ASTHMA
me_32727	re_H33z.11	HYPERREACTIVE AIRWAYS DISEASE
me_5267	re_H331.00	INTRINSIC ASTHMA
me_18323	re_H331111	INTRINSIC ASTHMA WITH ASTHMA ATTACK
me_58196	re_H331100	INTRINSIC ASTHMA WITH STATUS ASTHMATICUS
me_29325	re_H331000	INTRINSIC ASTHMA WITHOUT STATUS ASTHMATICUS
me_3665	re_H331.11	LATE ONSET ASTHMA
me_12987	re_H33z200	LATE-ONSET ASTHMA
me_10863	re_H36..00	MILD CHRONIC OBSTRUCTIVE PULMONARY DISEASE
me_25796	re_H332.00	MIXED ASTHMA
me_10802	re_H37..00	MODERATE CHRONIC OBSTRUCTIVE PULMONARY DISEASE
me_11150	re_H311.00	MUCOPURULENT CHRONIC BRONCHITIS
me_61513	re_H311z00	MUCOPURULENT CHRONIC BRONCHITIS NOS
me_12166	re_H3y..00	OTHER SPECIFIED CHRONIC OBSTRUCTIVE AIRWAYS DIS
me_7731	re_H330.14	POLLEN ASTHMA
me_40159	re_H311000	PURULENT CHRONIC BRONCHITIS
me_233	re_H33z011	SEVERE ASTHMA ATTACK
me_9876	re_H38..00	SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE
me_4892	re_H33z000	STATUS ASTHMATICUS NOS
me_93568	re_H39..00	VERY SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEA
pneumonia		
me_101204	re_H47..99	ASPIRATION PNEUMONIA
me_25054	re_H470.11	ASPIRATION PNEUMONIA DUE TO VOMIT
me_5324	re_H470312	ATYPICAL PNEUMONIA
me_23095	re_H28..00	BACTERIAL PNEUMONIA NOS
me_3683	re_H22z.00	BASAL PNEUMONIA DUE TO UNSPECIFIED ORGANISM
me_22835	re_H261.00	BRONCHIOLITIS OBLITERANS ORGANISING PNEUMONIA
me_886	re_H564.00	BRONCHOPNEUMONIA DUE TO UNSPECIFIED ORGANISM
me_29457	re_H25..00	CHEST INFECTION - INFLUENZA WITH PNEUMONIA
me_22795	re_H270.11	CHEST INFECTION - OTHER BACTERIAL PNEUMONIA

me_19400	re_H22..11	CHEST INFECTION - PNEMONIA DUE TO UNSPECIFIED O
me_29166	re_H26..11	CHEST INFECTION - PNEUMOCOCCAL PNEUMONIA
me_30653	re_H21..11	CHEST INFECTION - PNEUMONIA ORGANISM OS
me_16287	re_H23..11	CHEST INFECTION - UNSPECIFIED BRONCHOPNEUMONIA
me_9389	re_H25..11	CHEST INFECTION - VIRAL PNEUMONIA
me_104121	re_H20..11	COMMUNITY ACQUIRED PNEUMONIA
me_31643	re_H2B..00	CONGENITAL PNEUMONIA
me_103475	re_Q310.00	CRYPTOGENIC ORGANISING PNEUMONIA
me_104264	re_H564.11	HOSPITAL ACQUIRED PNEUMONIA
me_24356	re_H2C..00	HYPOSTATIC BRONCHOPNEUMONIA
me_23333	re_H540100	HYPOSTATIC PNEUMONIA
me_13573	re_H540000	INFLUENZA WITH BRONCHOPNEUMONIA
me_35745	re_H270000	INFLUENZA WITH PNEUMONIA NOS
me_4910	re_H270z00	INTERSTITIAL PNEUMONIA
me_1849	re_H56y100	LOBAR (PNEUMOCOCCAL) PNEUMONIA
me_9639	re_H21..00	LOBAR PNEUMONIA DUE TO UNSPECIFIED ORGANISM
me_13563	re_H260.00	OTHER ASPIRATION PNEUMONIA AS A COMPLICATION OF
me_28634	re_SP13100	OTHER BACTERIAL PNEUMONIA
me_11849	re_H22..00	OTHER SPECIFIED PNEUMONIA OR INFLUENZA
me_40299	re_H2y..00	PNEUMONIA - CANDIDAL
me_12061	re_AB24.11	PNEUMONIA - LEGIONELLA
me_10086	re_H22y200	PNEUMONIA AND INFLUENZA
me_43884	re_H2...00	PNEUMONIA DUE TO BACTERIA NOS
me_37881	re_H22yz00	PNEUMONIA DUE TO HAEMOPHILUS INFLUENZAE
me_48804	re_H222.00	PNEUMONIA DUE TO HAEMOPHILUS INFLUENZAE
me_23546	re_H222.11	PNEUMONIA DUE TO KLEBSIELLA PNEUMONIAE
me_1576	re_H220.00	PNEUMONIA DUE TO MYCOPLASMA PNEUMONIAE
me_52384	re_H231.00	PNEUMONIA DUE TO OTHER AEROBIC GRAM-NEGATIVE BA
me_50867	re_H22yX00	PNEUMONIA DUE TO OTHER SPECIFIED BACTERIA
me_25694	re_H22y.00	PNEUMONIA DUE TO OTHER SPECIFIED ORGANISMS
me_30591	re_H23..00	PNEUMONIA DUE TO PSEUDOMONAS
me_34251	re_H221.00	PNEUMONIA DUE TO SPECIFIED ORGANISM NOS
me_5612	re_H23z.00	PNEUMONIA DUE TO STAPHYLOCOCCUS
me_12423	re_H224.00	PNEUMONIA DUE TO STREPTOCOCCUS
me_63858	re_H223.00	PNEUMONIA DUE TO STREPTOCOCCUS, GROUP B
me_572	re_H223000	PNEUMONIA DUE TO UNSPECIFIED ORGANISM
me_6094	re_H26..00	PNEUMONIA OR INFLUENZA NOS
me_41034	re_H2z..00	PNEUMONIA WITH MEASLES
me_67901	re_H240.00	PNEUMONIA WITH NOCARDIASIS
me_60482	re_H24y100	PNEUMONIA WITH Q-FEVER
me_30437	re_H24y300	PNEUMONIA WITH WHOOPING COUGH
me_30509	re_H243.00	POST OPERATIVE CHEST INFECTION
me_34300	re_SP13200	POSTOPERATIVE PNEUMONIA
me_9953	re_H262.00	TUBERCULOUS PNEUMONIA
me_5202	re_A116.00	VIRAL PNEUMONIA

me_33478	re_H20..00	VIRAL PNEUMONIA NEC
me_14976	re_H20y.00	VIRAL PNEUMONIA NOS
me_53753	re_H20z.00	[X]OTHER PNEUMONIA, ORGANISM UNSPECIFIED
	re_Hyu0H00	
sepsis		
me_10872	re_A384200	ESCHERICHIA COLI SEPTICAEMIA
me_1703	re_A362.00	MENINGOCOCCAL SEPTICAEMIA
me_104150	re_A3Cy.00	OTHER SPECIFIED SEPSIS
me_57743	re_A272100	PASTEURELLA SEPTIC INFECTION (CAT OR DOG BITE
me_12400	re_A384300	PSEUDOMONAS SEPTICAEMIA
me_18809	re_A021.00	SALMONELLA SEPTICAEMIA
me_104028	re_A38z.11	SEPSIS
me_2136	re_A3C..00	SEPSIS
me_11690	re_L40..11	SEPSIS - PUERPERAL
me_104633	re_A3C2.11	SEPSIS DUE TO ANAEROBES
me_105102	re_A3C2.00	SEPSIS DUE TO ANAEROBIC BACTERIA
me_1288	re_N010.11	SEPTIC ARTHRITIS
me_885	re_A38..00	SEPTICAEMIA
me_31706	re_A383.00	SEPTICAEMIA DUE TO ANAEROBES
me_35232	re_A384.00	SEPTICAEMIA DUE TO OTHER GRAM NEGATIVE ORGANI
me_29950	re_A380000	SEPTICAEMIA DUE TO STREPTOCOCCUS, GROUP A
me_10978	re_A380100	SEPTICAEMIA DUE TO STREPTOCOCCUS, GROUP B
me_33765	re_A38z.00	SEPTICAEMIA NOS
me_23840	re_L090z00	SEPTICAEMIA NOS FOLLOWING ABORTIVE PREGNANCY
me_16104	re_A381.00	STAPHYLOCOCCAL SEPTICAEMIA
me_15229	re_A380.00	STREPTOCOCCAL SEPTICAEMIA
me_54077	re_H5y0100	TRACHEOSTOMY SEPSIS
me_37043	re_Q404z00	UMBILICAL SEPSIS NOS
me_104141	re_K190600	UROSEPSIS

MIMIC-III

Code and code lists for the MIMIC-III studies can be found in the following repository:

https://github.com/MIT-LCP/mimic-code/tree/7ff270c7079a42621f6e011de6ce4ddc0f7fd45c/concepts