SEQUELAE OF SELECTED GASTROINTESTINAL INFECTIONS: INCIDENCE, RISK FACTORS, AND ECONOMIC IMPACT ON THE NATIONAL HEALTH SERVICE IN ENGLAND

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Abstract

Background Sequelae of reactive arthritis (ReA), irritable bowel syndrome (IBS), Guillain-Barré syndrome (GBS), ulcerative colitis (UC), Crohn's disease (CD) and Rheumatoid arthritis (RA) following gastrointestinal (GI) infections can occur. Evidence suggests proton pump inhibitors (PPI) or antibiotics can increase the risk of GI infections, but their role in sequelae onset is unclear. Further, the impact on the National Health Service (NHS) of GI infections sequelae is unknown.

Methods Four studies were conducted in this thesis. First, a systematic review (SR) to determine the association between prior use of PPI or treatment with antibiotics and the onset of ReA and IBS amongst patients with *Campylobacter* or non-typhoidal *Salmonella* (NTS) infections. Second, a population-based study of routinely collected linked primary care, hospital, deprivation and deaths data (2000-2015) to determine the incidence of ReA, IBS, GBS, UC, CD, and RA in the 12 months following *Campylobacter* or NTS infection. Third, a retrospective cohort study to assess the role of antibiotics or PPI in the onset of sequelae amongst patients with *Campylobacter* infection. Fourth, an economic assessment to determine the impact of sequelae of the selected GI infections on the volume, type and costs of all health care encounters in the periods' pre- and post-infection.

Results In the SR, only one study reported an elevated risk in the onset of ReA amongst patients with the selected GI infections who had prior PPI prescription. There was no clear association between antibiotics and sequelae onset. In the population-based study, less than two per cent of the patients developed sequelae. Patients with sequelae were mainly females in comparison with those with GI infection only. Of all the sequelae considered, the incidence of IBS was highest in the 12 months post-infection (1.2%). Female *Campylobacter* patients on PPI were two and a half times more likely to develop IBS. There was no association with antibiotics and the onset of sequelae of campylobacteriosis. Sequelae significantly impacted the NHS with an additional £1.3 million in expenditure on average annually. Males, older people (65+), and those with underlying health conditions incurred the highest costs.

Conclusions The findings raise the need to emphasise the negative consequences of *Campylobacter* and NTS infections. It highlights the significant impact of sequelae on the NHS and the patient groups with excess expenditure. This is vital in the evaluation of public health interventions to reduce the overall burden of these GI infections. Further evidence to determine the existence of a dose-response relationship between PPI and *Campylobacter* infection in the onset of IBS is warranted.

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Role of the author

I declare that the work presented in this thesis is my own. Where information has been derived from other sources, this has been indicated and appropriately referenced.

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Rapid Fire Poster (5 minutes): **Esan O.** Bespoke linkage of Public Health England data on gastrointestinal infections to the Clinical Practice Research Datalink: ethics approval and a

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Poster Presentations

Esan O.Cohort profile of patients with gastrointestinal infections from the Clinical Practice Research Datalink (Public Health England Research and Applied Epidemiology Scientific Meeting, Warwick 2017)

Abbreviations

ACROBAT_NRSI	Cochrane Risk of Bias Assessment Tool: for Non-Randomised Studies of Interventions
BNF	British National Formulary
C.I	Confidence interval
CAG	Confidential Advisory Group
CAG	Confidential Advisory Group
CD	Crohn's disease
CPRD	Clinical Practice Research Datalink
DHSC	Department of Health and Social Care
DRG	Disease-related group
EHR	Electronic health record
FCE	Finished consultant episode
FLG	Faecal and lower gastrointestinal tract
GBS	Guillain Barré syndrome
GI	Gastrointestinal
GP	General Practitioner
GPRD	General Practice Research Database
FD	Functional dyspepsia
HES	Hospital Episode Statistics
HPA	Health Protection Agency
HRA	Health Research Authority
HRG	Healthcare resource group
HRG	Healthcare resource group

HUS	Haemolytic uraemic syndrome
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
ICD	International Classification of Diseases
IID	Infectious intestinal disease
IG	Information governance
IMD	Index of multiple deprivation
ISAC	Independent Scientific Advisory Committee
LSOA	Lower super output area
MCCD	Medical certificate cause of death
MHRA	Medicine and Healthcare products Regulatory Agency
NOIDS	Notification of Infectious diseases system
NTS	Non-typhoidal *Salmonella*
ONS	Office of National Statistics
OP	Outpatients
OPCS	Operation Procedure Classification System
OXMIS	Oxford Medical Information System
PCA	Prescription cost analysis
PCR	Polymerase chain reaction
PHE	Public Health England
PII	Patient Identifiable Information
PPI	Proton Pump Inhibitors
PSSRU	Personal Social Services Research Unit
PY	Person-years

RA	Rheumatoid arthritis
RCGP	Royal College of General Practitioners
ReA	Reactive arthritis
RS	Reiters syndrome
SES	Socio-economic status
SGSS	Second generation surveillance system
STEC	Shiga toxin producing *Escherichia coli*
UC	Ulcerative colitis
UK	United Kingdom
UTS	Up to standard
WHO	World Health Organization

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Chapter 1

Introduction

1.1 Overview

This chapter explains the rationale for the thesis from a personal point of view.

1.2 Surveillance of gastrointestinal infections in England

My first experience in the surveillance of gastrointestinal (GI) infections was in the monitoring and outbreak detection of non-typhoidal *Salmonella* (NTS) infections in England at the Health Protection Agency, now Public Health England (PHE). As there was no enhanced surveillance for NTS infections, monitoring and outbreak detection was limited to laboratory reports. Investigations soon felt like a "fire-fighting" service as we could only react to attempt to stop an outbreak by which time incident cases would have dropped, preventing any analytical study from confirming possible risk factors for the incident. The lack of risk factor and clinical information in the current data structure was frustrating considering my background in "experimental" microbiology where it was possible to generate more data that can be easily assimilated, thanks to the advancement in the technology.

Although one could argue that NTS is on the decline in most Western countries, so why should funds be invested in the control of an infection that was not a significant cause of disease [1,2]? Conversely, *Campylobacter* was and is still on the increase, but there was also no enhanced surveillance in place [3]. In 2009, there was a large outbreak of shiga-toxin producing *Escherichia coli* (STEC) on an open farm in Godstone, Surrey in the South-East of England which affected 76

children, with over a third requiring hospitalisation (35%, 27) and 17 developing haemolytic uraemic syndrome (HUS), a severe kidney disease [4]. An enquiry into the outbreak investigation found that General Practitioners (GPs) did not immediately suspect STEC infection in children with infectious bloody diarrhoea [4]. Since the study, changes were made to the mandatory reporting of notification of infectious diseases in the Health Protection Regulations Act of 2010 to include HUS and infectious bloody diarrhoea, changing the perceived risk of STEC infection [5]. Although the rate of infection is low, the impact is high with severe consequences. We do not want another Godstone incident before we reassess the perceived risks of NTS and *Campylobacter* infection. Reconciling the microbiological, epidemiological, and clinical information on patients with these infections will address any existing gap in the consequences of these infections.

1.3 The motivation for the thesis

Previously, I was a Public Health Analyst with the West Midlands Public Health Observatory, now part of PHE. The role involved analysis of secondary sources of data such as hospitalisation and deaths records. Linkage of these records to other datasets is now routine. The opportunity to link these datasets to PHE's surveillance data piqued my interest in the studentship. I hope to address the gap in existing surveillance information with linked individual patient records across their entire health journey. The potential to quantify and identify patients who are prone to sequelae of GI infections and the resulting economic impact on the NHS will aid policymakers in directing scarce resources.

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Chapter 2

General Background

2.1 Overview

This chapter provides an overview of the epidemiology of bacterial causes of gastrointestinal infections and resulting sequelae globally and in England. The rationale for the thesis, aims and objectives, and the structure of the thesis are also stated.

2.2 Gastrointestinal infections

Gastrointestinal (GI) infections remain a significant cause of morbidity and mortality worldwide affecting up to 2 billion people leading to 1 million deaths annually [1]. Children below the age of 5 and those living in low-income countries bear the highest burden [1]. In high-income countries such as the United Kingdom (UK), the focus of this thesis, morbidity rather than mortality is the pressing issue.

Many enteric pathogens (bacteria, viruses and protozoa) cause GI infections with varied host susceptibility, disease progression and clinical spectrum. The most commonly reported symptoms include gastroenteritis, an inflammation of the stomach and small intestine; diarrhoea, vomiting and abdominal pain. If pathogens evade the bloodstream, then systemic manifestations such as septicaemia and even death can occur. *Campylobacter* is the most common bacterial cause of GI infections globally, while non-typhoidal *Salmonella* (NTS) is responsible for the most deaths [2,3].

Several terminologies are used to refer to GI infections such as foodborne diseases, food poisoning, acute gastroenteritis and infectious intestinal diseases (IID) depending on the context and scope of the aetiology under study. Not all GI pathogens such as *Clostridium perfringes, Listeria monocytogenes*, and *Helicobacter pylori* will cause gastroenteritis in humans. Moreover, an accurate definition of a foodborne disease requires source attribution to adequately quantify the proportion of GI infections which occur following consumption of contaminated food or water. While, the term "food poisoning" is not restricted to GI infections only, because chemicals, heavy metals and mycotoxins are not infectious but can cause food poisoning if ingested.

IID is a subset of both gastrointestinal infection and gastroenteritis since it is always characterised by gastrointestinal symptoms [4]. GI infections and IID are used interchangeably in this thesis, and both refer to acute episodes of diarrhoea and vomiting following the infection of an enteric/GI pathogen.

2.2.1 Common bacterial causes of GI infections

This thesis focuses on *Campylobacter* and NTS as exemplary pathogens in bacterial causes of GI infections in England as *Campylobacter* is the most common bacterial GI pathogen in England. It is frequently detected amongst patients who present to healthcare. As a result, data is readily available to establish a cohort for long term follow-up. While NTS is the leading cause of death following GI infections globally. Further, these two pathogens represent the priority organisms for the UK Food Standard Agency (FSA) in reducing microbial contamination along the food chain [5].

Campylobacter spp. are Gram-negative bacteria with a genus of 26 species, two provisional species, and nine subspecies [6]. *C. jejuni* and *C. coli* are the most common species of *Campylobacter* infections in humans. However other species such as *C. concisus*, *C. ureolyticus*, *C. upsaliensis*, and *C. lari* are now emerging which may be an artefact of improved detection [7,8].

Salmonella enterica is another Gram-negative bacterium with six subspecies. Subspecies I is responsible for 95% of all human and animal diseases [9]. Further differentiation based on antigenic presentation has identified over 2,600 different serovars (serotypes) to date [10]. These serovars are broadly divided into typhoidal and NTS. Typhoidal serovars cause an invasive, life-threatening and systemic disease known as enteric fever and are endemic in low-income countries that lack clean water and adequate sanitation [11].

In contrast, NTS in humans usually induces gastroenteritis and is more widespread globally [9]. *Salmonella enterica* subsp. *enterica* serovars Enteritidis and Typhimurium are the most frequently (27% and 20% respectively) isolated serotypes in the UK, and some serovars of NTS (5%) can also cause invasive disease in both immunocompromised and otherwise healthy people [10].

2.2.2 Detection of *Campylobacter* and NTS infections

There are several methods available to identify *Campylobacter* or NTS in patients with suspected GI infections. These are broadly divided into culture-dependent and culture-independent tests. In culture-dependent tests, selective media, temperature, incubation time, and atmospheric conditions can be altered to favour growth [12]. However, these enrichment conditions do not always increase the yield of the isolates, which can be affected by the initial bacterial load in the specimen, the timing between the onset of disease, preparation and transport of the specimen [12].

Increasingly, culture-independent tests which include antigen-based tests and molecular tests are being adopted for GI infections owing to their increased sensitivity, specificity, rapid turnaround time, ability to detect multiple pathogens in one test, lower cost, and less technical expertise in comparison to culture-dependent methods [12,13]. The most commonly used molecular tests are the nucleic acid amplification tests, which include polymerase chain reaction (PCR) [13]. Adopting these non-culture methods for *Campylobacter* can increase the detection of fastidious species such as *C. concisus*, *C. ureolyticus*, *C. upsaliensis*, and *C. lari,* reducing the proportion of undetected samples [7].

However, culture remains the standard process of accurate identification and recovery of *Campylobacter* and NTS infections because isolates are still needed for advanced genetic characterisation to identify clusters, outbreaks, and emerging infections for public health surveillance [7,13].

2.2.3 Transmission of *Campylobacter* and NTS infections

Both *Campylobacter* and NTS infections are zoonotic, i.e. originate from animal reservoirs, and can spread to humans through the faecal-oral route. Exposure can be direct through person-person transmission as a result of poor hand hygiene or indirect through the ingestion/handling of contaminated foods such as eggs and raw meat of pork and poultry [14]. Both pathogens can persist in the environment, as such, farming activities, handling of domestic animals and foreign travel can be associated with disease [14].

Not all exposure will lead to a clinically relevant disease. Some people may develop a mild or moderate disease without the need for medical contact or intervention with others requiring medical attention for severe illness, and in some cases, death occurs. Disease severity and onward transmission to others are dependent on the combination of host susceptibility to infection and virulence of the agent [15].

2.2.4 Treatment of *Campylobacter* and NTS infections

The illness is self-limiting in most people, hence treatment is only indicated if patients are systemically unwell [4]. Fluoroquinolones are occasionally used for prophylaxis against travellers' diarrhoea, i.e. GI infection acquired by foreign travel to an area where the infection is endemic. If travel is to an area where resistance to fluoroquinolones is endemic such as South-East Asia, azithromycin, a type of macrolide is recommended [16]. According to the guidelines in England, where *Campylobacte*r is the known aetiology, treatment with quinolones/macrolides can reduce the duration of diarrhoea (2.4 vs 4 days) if started within three days of symptom onset [17,18]. However, the increase in resistant strains has led to cautionary advice in their use, and quinolones are no

longer recommended for treatment [19]. Antibiotics do not appear to be beneficial in otherwise healthy adults for NTS as treatment can lead to persistent colonisation [20]. Anti-motility drugs such as loperamide are sometimes prescribed for mild/moderate traveller's diarrhoea to help alleviate the symptoms [21].

2.2.5 Epidemiology of GI infections in the United Kingdom

The epidemiology in England broadly follows the pattern and rates in the UK. According to the second study of IID (IID2) conducted in 2008-2009, the community level incidence (incorporating those who seek healthcare and those who do not) of all known causes of IID was 274 cases per 1000 population (95% confidence interval [C.I], 254-296) [4]. This means around 17 million cases or 25% of the UK population have an episode of IID annually. Thus, more people are affected by IID a decade on from the first study (IID1) conducted in 1993-1996 in England where the incidence in the community was 194 cases per 1000 population, or 9.4 million (20% of England) people experiencing an episode of IID annually [4,22].

Although the elevated increase was due to viral causes of IID, bacterial causes remain a substantial burden [23]. *Campylobacter spp.* is the most common bacterial cause of GI infection in the UK. Levels have remained stable for over ten years, IID1(8.7 cases per 1000 person-years (95% CI, 6.1-12.3), and IID2 (10 cases per 1000 person-years 95% CI 6.3-15.8), with up to half a million cases in the community annually [4,22]. Amongst cases presenting to healthcare, *Campylobacter* is the most frequent bacterial cause of gastroenteritis with up to 80,000 primary care consultations annually. In contrast, NTS appears to be declining with a marked drop in GP presentation, 1.6 cases per 1000 person-years (95% C.I, 1.2–2.1) in IID1 to 0.2 cases per 1000 person-years (95% C.I, 0.1–0.5) in IID2 and a lesser but still substantial decline in estimated community cases (2.2 per 1000 person-years (95% C.I, 1.1–4.3 for IID1 to 0.7 cases per 1000 person-years (95% C.I, 0.2–3.0) in IID2) [24].

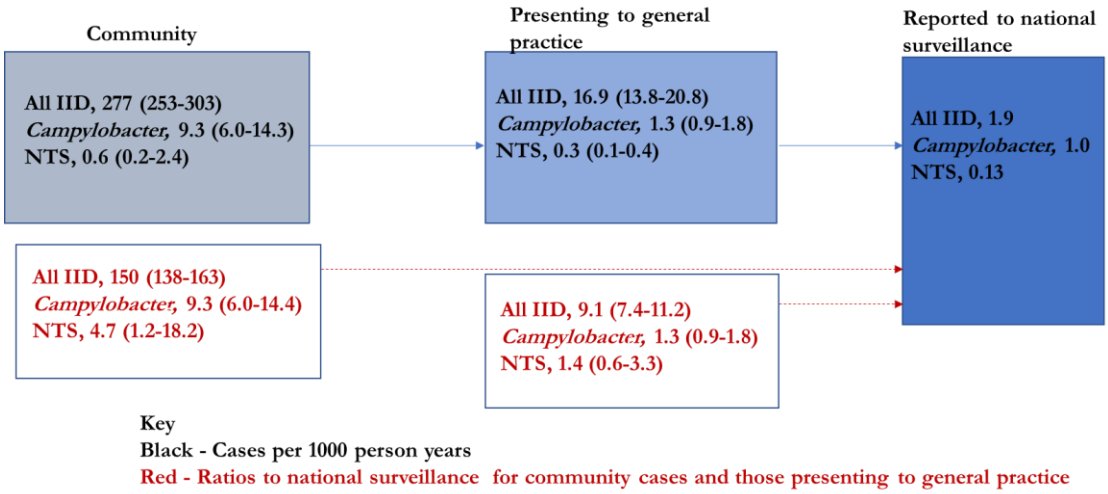
There were no changes in the overall age and sex distributions between the two iterations of the IID studies [4]. Children are disproportionately affected especially those under the age of 5, with

infants expected to have at least an episode of IID annually (1,079 per 1,000 person-years, 95% CI, 750.1-1553.3) [4]. Although the rate of IID was lower in older people aged 65 and above, they have a three-fold increase (hazard ratio = 3.08, 95% C.I, 2.54-3.74) of recurrent episodes following their initial episode of IID [25]. Women aged 25-34 years (387 per 1,000 person-years, 95% C.I 304.9 - 492.2) experience a higher rate of IID compared to men of the same age (184 per 1,000 person-years, 95% C.I 102 - 332.5) [4].

2.2.6 Surveillance of GI infections in England

Surveillance is information for action. The need to detect, monitor and reduce the burden of disease is the primary driver. In England, the surveillance of GI infections such as *Campylobacter* and NTS is primarily based on laboratory data held by PHE. This data is described in detail in Chapter 4. It consists of both compulsory positive laboratory returns of GI pathogens that cause food poisoning, HUS and bloody diarrhoea as part of the statutory notifications of infectious diseases (NOIDS), and voluntary positive results of other GI infections not part of the NOIDS sent by local laboratories to the national surveillance [26]. PHE laboratory data only captures cases presenting to healthcare who are most likely to have a more severe illness and does not contain any additional risk factor information or patient's clinical histories [27]. Therefore, surveillance data alone underestimates the total burden of GI infections. Although IID2 study was conducted for the entire UK population, IID rates for England were also estimated to recalibrate the level of underreporting of IID in national surveillance and produce updated ascertainment ratios between all IID in the community, those presenting to healthcare and those captured by national surveillance. These ascertainment ratios were used to produce robust estimates of incidence, and they demonstrated that for every case of IID reported to national surveillance, there were 147 cases in the community (Figure 2-1) [4].

Figure 2-1 Ascertainment ratios for IID in England, comparing rates in the community, presenting to general practice and reported to national surveillance from IID2 study, 2008-2009



Source: Adapted from Tam et *al.* (2011). The second study of infectious intestinal disease in the community (IID2 Study). Final report [4]. Ascertainment ratios are shown for England only. Not all cases in the community will present to primary care, and not all cases presenting to general practice will be reported to the national surveillance. The ratios show the level of underreporting between cases in the community and those presenting to primary care with the cases reported to national surveillance. 95% confidence intervals in brackets.

2.3 Sequelae of *Campylobacter* and NTS infections

Intestinal complications of irritable bowel syndrome (IBS), inflammatory bowel disease manifested as either Crohn's disease (CD) and ulcerative colitis (UC), and extra-intestinal manifestations such as reactive arthritis (ReA), Guillain-Barré Syndrome (GBS), rheumatoid arthritis, endocarditis, pericarditis pancreatitis, nephritis, and appendicitis have been reported following *Campylobacter* and NTS infections [28–31].

Chronic abnormal bowel movement is the main clinical feature of IBS. It is a functional disorder of the gut characterised by alternating symptoms of abdominal pain, constipation, bloating and diarrhoea [32]. It is usually diagnosed in primary care settings based on clinical criteria due to the absence of a biochemical or an inflammatory marker, with an estimated prevalence of 11% globally

[32]. In contrast, IBD in the form of Crohn's disease (can affect the entire GI tract from the mouth to the anus) or ulcerative colitis (inflammation of the colon) requires further investigations under the care of a specialist (gastroenterologist) to assess the severity of the disease and determine treatment options [33].

ReA, which is an inflammation of the joints, is also commonly diagnosed in primary care settings. A systematic review using cohort studies reported a higher incidence of ReA following salmonellosis in comparison to campylobacteriosis (12 ReA cases per 1000 salmonella infection cases; 95% CI 11-13 vs 9 ReA cases per 1000 *Campylobacter* infection cases; 95% CI 9-10) [34]. The authors included primary studies that reported a range of follow-up period across studies and diagnosis was based on surveys with low response rate. Therefore, ReA following enteric infection may be underreported. In contrast, GBS, an autoimmune condition characterised by rapid onset muscle weakness as a result of the immune system damaging the peripheral nervous system, is usually diagnosed in secondary care settings [35]. It occurs at an estimated rate of 30.1 GBS case per 100,000 campylobacter cases generally within 14 days of infection and up to two months in some cases [36,37].

NTS is the leading cause of death from a bacterial GI pathogen in the UK and other high- income countries with 119 deaths reported in the UK in 2000 [2,38]. However, the incidence of NTS has changed dramatically in the UK, and the estimate was derived from data collected over 20 years ago and [39]. Hence, current estimates of deaths are required to inform ongoing strategies in reducing NTS infections.

Risk factors associated with sequelae following GI infection are not well understood. Certain species of *Campylobacter* and serovars of NTS are known to be more invasive than others [2,7,38]. Age and sex are probable risk factors. Male elderly patients may have an elevated risk for GBS, while IBS is shown to occur more in females following *Campylobacter* infection [32,34,40].

Drugs which increase gastric pH and change gut flora such as proton pump inhibitors (PPI) and antibiotics can increase the susceptibility to GI infection [41,42]. Where studies have considered the role of these drugs as potential risk factors in the onset of GI infections, there is limited evidence of their role in sequelae development [20]. For instance, PPI usage was associated with repeated gastroenteritis episodes and subsequent development of ReA following campylobacteriosis in a case-control study in The Netherlands, although findings were limited by low response rate [43]. While some studies have reported an increased risk of ReA following antibiotics usage, others report a protective effect, and in some studies, no effect was observed [44–46]. These conflicting findings highlight the uncertainty in the risk of sequelae following antibiotics or PPI usage and the need for further investigations.

2.4 Disease burden and costs of *Campylobacter* and NTS infections

Estimates of sequelae of GI infections are essential in determining the actual burden of these infections. Globally, NTS is responsible for the highest DALY (4.1 million, 95% uncertainty interval 2-49-6.27 million) in 2010 [1]. The DALY is the Disability Life Adjusted Years metric used to measure overall disease burden, expressed as the years lost due to illness, disability or death [47]. The economic burden that illness imposes on society and individuals is estimated in a cost of illness (COI) study [48]. It considers the incidence or prevalence of disease and its effect on morbidity, longevity, quality of life, and financial aspects including direct and indirect expenditures that result from injury, comorbidities, any disability, or premature death [48].

In the case of GI infections, capturing all costs incurred by patients, the health service and wider society at large requires multiple data sources which vary in availability and quality. The most recent pathogen-specific cost estimates using IID2 data reported lower overall societal costs of *Campylobacter* disease (£50 million) in comparison with IID1 (£70 million), despite a stable incidence of campylobacteriosis [49]. Stratification by healthcare usage revealed the decrease in cost

were due to reductions in GP usage; IID-related GP consultation rates halved between 1995 and 2009 [49]. This reduction in GP usage also reduced the cost per case (from £164 in IID1 to £85 in IID2). Cost estimates were only available in IID1 for NTS patients. Total costs attributed to NTS infections were lower (£46.4 million) than *Campylobacter* infections. However, costs to NHS hospitals were over three times higher for NTS patients (6.4 million) in comparison with *Campylobacter* patients (1.9 million) [50].

Both IID1 and IID2 based cost estimates included primary care and hospital encounters and direct out-of-pocket expenses of cases such as transportation to a hospital, costs of accompanying carers, and time off from employment. Costs to the wider society from mortality and illness in caregivers were not included as these data are sparse. Although IID2 based estimates incorporated costs from GBS as a sequela of *Campylobacter* infection, costs were not further stratified according to age, sex, socio-demographic factors, severity, or existing co-morbidities to reflect the highly significant variation in related costs across cases [48].

Campylobacter is a top priority pathogen in the FSA foodborne disease strategy with the implementation of a new risk management programme [5]. NTS is also a high FSA policy agenda. It is one of the target organisms in the reduction of zoonoses transmitted through the food chain [5]. The current estimates of the cost of illness for both *Campylobacter* and NTS provide useful background or baseline data for economic evaluations of the cost-effectiveness of ongoing interventions to reduce the overall burden of these infections. However, in the absence of the resource use and costs estimates incurred before these GI infection, the absolute impact of both *Campylobacter* and NTS infections on resource use and associated costs to the NHS is not possible. This measure of absolute difference is crucial in understanding the opportunity foregone by the payer (NHS) in addressing the consequences of *Campylobacter* and NTS infections. Further, stratification of COI estimates at the patient-level allows the exploitation of patient-level

heterogeneity in the predisposition to disease, to enable efficient allocation of resources, and targeted prevention strategies.

2.5 The rationale for thesis, aims and objectives

2.5.1 Evidence Gaps

The lack of evidence on risk factors associated with sequelae of *Campylobacter* and NTS infections highlights the need for primary research to fill this gap in knowledge. Published studies to date adopted cohort studies, case-control studies and systematic reviews; they used primary data collection from the community, laboratory, GP consultation and hospitalisation records to determine the burden of these GI infections and assess potential risk factors in the severity of illness and sequelae. Patient records were unlinked in these studies. As a result, following patients across the different healthcare settings in estimating the burden of sequelae following these GI infections is precluded j[34,42,43,51–53].

Attempts to quantify the burden of GI infections were made with both iterations of the IID studies. Both studies were able to estimate the level of GI infections in the community, while the second study recalibrated the level of underreporting of GI infections, thus providing a robust estimate of the burden of infection in the community [24]. The second study used a range of prospective and retrospective studies combining several sources of data recording illness but not linking them directly. The main sources of data used were laboratory and primary care data. Secondary care data was not included. Although other studies using IID2 data have reported GBS as a sequela of *Campylobacter* infection in the UK, the incidence of sequelae was not reported in the main IID2 study and recently published estimates are unavailable.

2.5.2 Rationale

As previously mentioned (section 2.2.6), the surveillance of GI infections is primarily based on laboratory data. Information on symptom severity, treatment of infection, and subsequent sequelae are not captured by this data source. Assembling cohorts for long-term follow up to establish causality in the aetiology of the disease under study is the ultimate gold standard in epidemiology. However, these cohorts are usually expensive to set up and maintain.

Further, conclusive results for rare outcomes are not typically available until several decades after the study began. The increase in computational power at a relatively affordable cost allows the linkage of existing electronic health records (EHR) to create large cohorts for follow-up relatively quickly. This linked cohort enables researchers to address questions that are beyond a single data source.

In the UK, the Clinical Practice Research Datalink (CPRD), a primary care database with deterministic record linkage functionality to other routine healthcare and administrative records, provides a platform for addressing a range of public health and health service questions not possible with a single data source [54]. Established routine linkages include secondary care data, cancer registry data, mortality and administrative data such as deprivation data. Bespoke linkages to CPRD is also possible pending ethical approval.

Record linkage of existing EHR such as CPRD provides a powerful resource to estimate the incidence of sequelae following *Campylobacter* and NTS infections and the associated risk factors such as the use of antibiotics or PPI by exploring the continuity of care of patients across primary and secondary care settings. Up until now, studies in England are yet to explore this.

For this thesis, PHE surveillance data on *Campylobacter* and NTS infections, secondary care patient-level records - the Hospital Episode Statistics (HES), deaths record - Office of National Statistics (ONS) mortality data and the English Index of Multiple Deprivation (IMD) were linked to follow

up patients captured by national surveillance in the development of sequelae and to quantify any deaths that occurred. To determine the incidence of sequelae of *Campylobacter* and NTS infections and the associated risk factors amongst patients presenting to general practice, patients with the selected GI infections from CPRD were linked to HES, ONS mortality, and IMD data. Further, the impact of these selected GI infections and resulting sequelae on the volume, type and costs of health care resources used across both primary and secondary healthcare settings were assessed. Linkage of both PHE data and CPRD data to IMD permits the assessment of differences in the risk of poor outcomes across socio-economic groups.

This programme of work will provide up-to-date and robust estimates on the incidence of sequelae following *Campylobacter* and NTS infections, potential risk factors, and the economic impact on the NHS. These estimates can be incorporated into microbial risk models such as source attribution models of foodborne diseases to elucidate the actual burden of foodborne illness. Further, it will provide the baseline data for future economic modelling in evaluating the cost-effectiveness of current public health interventions in reducing the overall burden of disease.

2.5.3 Aims and objectives

The overall aim of this thesis is to address the knowledge gaps identified in this chapter by determining the incidence of sequelae of *Campylobacter* and NTS infections, the associated risk factors, and the economic impact on the NHS in England. Identifying these evidence gaps will provide a more robust estimate of the current burden of *Campylobacter* and NTS infections in England. This will inform policymakers in the evaluation of current interventions to reduce the overall burden of these GI infections.

2.5.4 Specific objectives

A. To review existing literature on sequelae following *Campylobacter* and NTS infections to identify key research gaps (Chapter 3).

B. To identify the distribution of sequelae of campylobacteriosis and salmonellosis across different ages, sex and regions in England using linked patient records; primary and secondary care data, and laboratory and secondary care data (Chapter 5).
C. To determine the risk factors associated with sequelae amongst individuals diagnosed with *Campylobacter* and NTS who may or may not have used antibiotics (macrolides, quinolones or cephalosporins) or PPI before and after their GI infection (Chapter 6).
D. To quantify the volume, type and costs of health care resources associated with sequelae of *Campylobacter* and NTS infections (Chapter 7).

2.6 The overall structure of the thesis and studies to address objectives

An overview of the studies within this thesis is illustrated in Figure 2-2. A brief description of the chapters is presented below.

Chapter 3: Factors associated with sequelae of *Campylobacter* and non-typhoidal *Salmonella* infections: a systematic review

This chapter identifies the existing research evidence on the incidence of sequelae following the selected GI infections with emphasis on symptom severity, use of antibiotics, or PPI as factors associated with the development of sequelae based on published data from observational studies.

Chapter 4: Methodology and research tools

This chapter outlines the data sources, the process for ethics approval, and the study design for the results presented in Chapters 5, 6, and 7.

Chapter 5: The incidence of sequelae of selected gastrointestinal infections

This chapter describes the characteristics of patients with *Campylobacter* and NTS infections selected from the primary care records. It provides the incidence of sequelae following these

selected GI infections in England and the characteristics of patients who develop sequelae. In the absence of direct linkage of primary and secondary care data to national surveillance data, national surveillance data in England were linked to hospitalisations data, and estimates of the incidence of sequelae and patient's characteristics from this data source were compared with estimates from the cohort of patients selected from primary care.

Chapter 6: Risk factors associated with the onset of sequelae following *Campylobacter*

The incidence estimates derived from the linked primary care data (Chapter 5) were explored further to determine the association, if any, of prescription of antibiotics or long-term use of PPI in the development of sequelae and to identify which patients are most at risk.

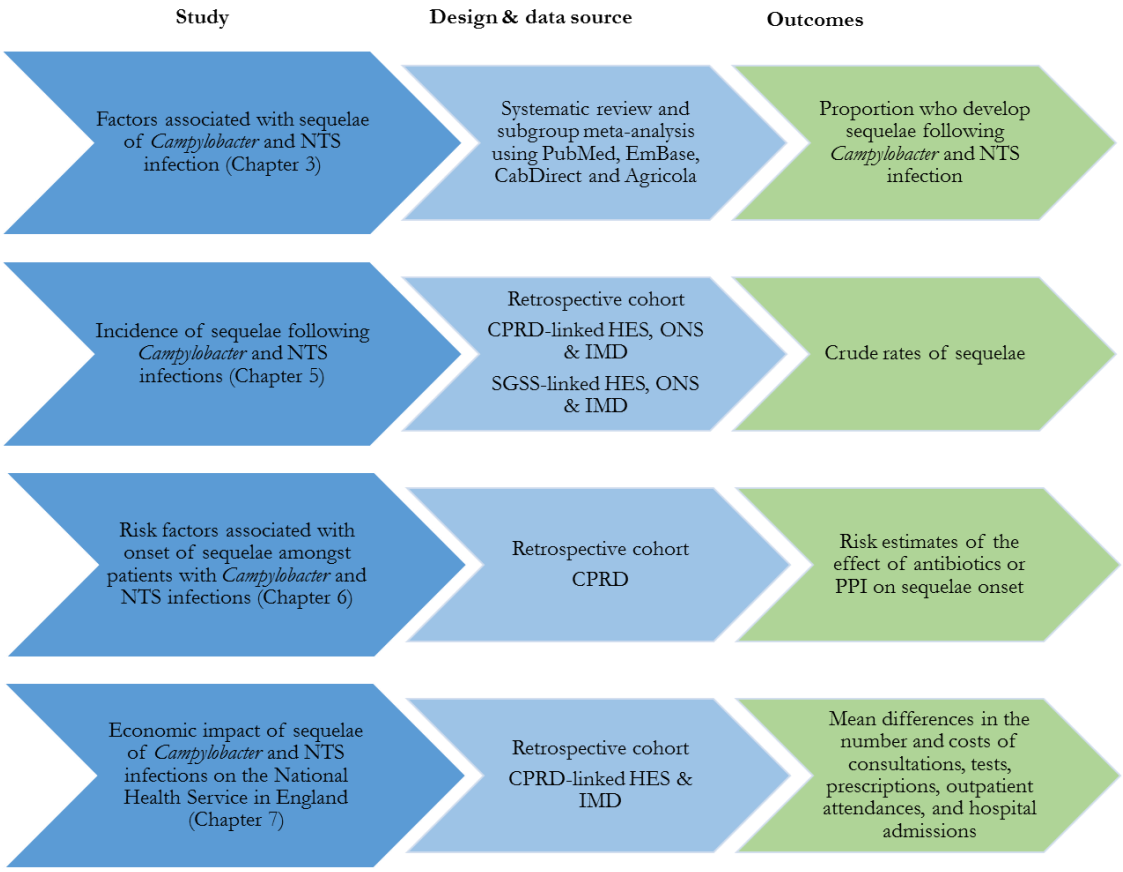
Chapter 7: Economic impact of sequelae of *Campylobacter* and non-typhoidal *Salmonella* infections on the National Health Service in England

The richness of the linked primary care data allowed a complete evaluation of direct healthcare costs incurred following the selected GI infections and subsequent sequelae. This provides a clear picture of the volume, and type of healthcare resources utilised and the associated costs directly due to a diagnosis of *Campylobacter* and NTS infections and the development of sequelae.

Chapter 8: Discussion

An overall summary of the main findings from each empirical study, overall study design, and relevance to published studies, implications for clinical practice, policy, public health and conclusions are presented here.

Figure 2-2 overview of studies within this thesis



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Chapter 3

Factors associated with sequelae of *Campylobacter* and Non-typhoidal Salmonella infections: A systematic review

3.1 Overview

This chapter describes the rationale for the systematic review, methods, results, discussion and implications for the empirical studies included in this thesis. Findings from the systematic review were published in a peer review journal, and the role of the co-authors are outlined where relevant.

3.2 The rationale for the systematic review topic

Systematic reviews have been conducted to assess the evidence of reported sequelae following GI infections but none of the studies assessed possible modifiable factors associated with the occurrence of sequelae as previously described in Chapter 2.

A series of meta-analyses were published in 2014 and 2015 to determine the proportion of *Campylobacter,* NTS and *E.coli* O157 cases who developed chronic sequelae [1-3]. The authors found a high degree of heterogeneity across studies, which could not be explained by subgroup analysis. Only the effect of study design factors such as follow-up time, group size, study directionality and method of assessing sequelae were considered. Host-related factors such as age, ethnicity, the severity of the acute illness, medical history and pathogen-related factors such as virulence were not assessed.

Modifiable factors contributing to the development of *Campylobacter* and NTS infections but not sequelae have been assessed in systematic reviews. These include the use of antibiotics in the treatment of the primary GI infection and the prior use of PPI, as described in Chapter 2 (section 2.3). Antibiotic therapy resulted in early negative stool cultures but higher rates of relapse afterwards in the treatment of NTS infections[4]. The review included studies of randomised control trials. However, the authors were unable to assess the effects of antibiotic therapy on NTS infection in high-risk groups such as infants, elderly and immunocompromised. These high-risk groups and travellers to areas where GI infections are endemic are those for whom treatment with antibiotics is indicated as it not recommended for healthy individuals due to the self-limiting nature of the illness [5].

The association of PPI in the onset of GI infections was first assessed in a meta-analysis, which suggested an increased risk of infection following acid suppressive therapy in 2007 [6]. Only four studies on the use of PPI and onset of enteric infections were pooled with unexplained heterogeneity despite subgroup analysis. Another systematic review conducted in 2011 found an association between NTS infections and treatment with PPI, but it was based on only two case-control studies [7].

The studies described above represent recently published systematic reviews and meta-analysis on sequelae following GI infections and modifiable factors associated with risk of GI infections. The authors did not assess the modifiable risk factors which contribute to the development of sequelae. Therefore, the role of PPI or antibiotics in the development of sequelae remains unknown.

3.3 Methods

This systematic review and meta-analysis were conducted in line with the 'Meta-analysis of Observational Studies in Epidemiology' (MOOSE) guidelines [8]. The protocol was registered on PROSPERO (CRD 42015026042) [58]. The systematic review was conducted with other colleagues (Oliver van Hecke - OVH, Madison Pearce - MP, Dylan Collins – DC and Thomas Fanshawe (TF). The role of each co-author is described in the relevant section.

3.3.1 Search strategy

A systematic search of four electronic databases, PubMed, Agricola[http://agricola.nal.usda.gov/], EMBASE [OvidSP] (1974-2016 April 27) and CabDirect [OvidSP] (2000 to 2016 Week 15) for studies reporting sequelae of ReA, RS, IBS, GBS, IBD, CD and UC following selected GI infections (*Campylobacter* or NTS) was conducted. The search strategies consisted of a combination of relevant Medical Subject Headings (Mesh) terms and free-text words in the title and abstract for exposure and outcome. Following a re-run of the searches and validation of studies included in previous systematic reviews, the last search was restricted to studies published between 01 January 2011 and 29 April 2016 as this was an update and extension of previous reviews with searches up to July 2011 [3, 9]. The detailed search strategies and results for each of the databases are presented in Appendix 3-1. Additional eligible studies on *Campylobacter* and NTS infections and associated sequelae were sought by reviewing the reference lists of identified articles. No language restrictions were applied during the search.

3.3.2 Supplementary search

One study collected the relevant data required but did not publish it as this was not the primary outcome under study. The corresponding author was contacted, and a reminder sent six weeks later. The author replied with the relevant data.

3.3.3 Selection criteria

Two reviewers (OE, OVH – DPhil colleague) independently screened titles and abstracts for relevance. Studies were included if they were cohort (prospective or retrospective), case-control, surveillance report or cross-sectional studies, or outbreak investigations of people with *Campylobacter* or NTS infection, and reported the number or proportion of people who developed the sequelae of interest following *Campylobacter* or NTS infection. Studies were excluded if they: reported sequelae without evidence of a past exposure with *Campylobacter* or NTS infection; reported sequelae with only serological evidence of past exposure to pathogens; reported sequelae for multiple foodborne infections without a breakdown of the proportion/numbers by pathogen and sequelae; were case reports, case series or experimental studies such as randomised controlled trials and laboratory-based studies.

3.3.4 Data extraction and bias assessment

Data were extracted independently by two reviewers (OE and MP) using a standardized form. Inconsistencies were resolved through a consensus process, with any disagreement resolved by a third reviewer, TF. Additional data for the period before July 2011 from the previous systematic reviews were extracted as required [3, 9]. Data coding and categorisation were in accordance with the previous reviews or otherwise stated (Appendix 3-2) [3, 9]. The primary outcome was the number of cases who developed the specific sequelae of interest divided by the total number of *Campylobacter* or NTS cases.

The Joanna Briggs Institute Prevalence Critical Appraisal Tool was adapted to evaluate the quality of each study [10]. This tool was selected because of its flexibility to address the risk of bias across a variety of study designs, as commonly found in the study of incidence and prevalence. Other available tools include the Newcastle-Ottawa scale for observational studies, Hoy et *al.* 's Risk of bias tool, Downs and Black Instrument, and the Cochrane Risk of Bias Assessment Tool: for Non-Randomised Studies of Interventions (ACROBAT_NRSI)

which is now known as the Risk of Bias in Non-Randomised Studies – of Interventions (ROBINS-I), since the conduct of this systematic review [11-15]. These tools were not used because they were not suitable for systematic reviews including outbreak investigations (Newcastle-Ottawa scale) [11]; did not include sample size calculation (Hoy et al's Risk of bias tool) [12]; time-consuming with irrelevant components (Downs and Black Instrument) [13]; resource intensive and complicated in applying to the systematic review in question (ACROBAT-NRSI) [14].

Initially, a calibration exercise was performed by review members using a random sample of three studies. The items in the tool were applied to the selected studies to ensure consistency across reviewers and validity in assessing the risk of bias with this tool. Following this exercise, two additional questions were included (Chapter 3 – Box 1). Inconsistency was resolved through a consensus process.

Chapter 3 – Box 1 Questions from The Joanna Briggs Institute Prevalence Critical Appraisal Tool

Q1. Was the sample frame appropriate to address the target population?
Q2. Were study participants sampled in an appropriate way (use of relevant data sources)?
Q3. Was the sample size adequate?
Q4. Were the study subjects and the setting described?
Q5. Was the data analysis conducted with sufficient coverage of the identified sample?
Q6*. Were valid methods used for the identification of the pathogen?
Q7. Were valid methods used for the identification of the complication?
Q8*. Was the pathogen measured according to standard practice for all participants?
Q9. Was the complication measured according to standard practice for all participants?
Q10. Was there an appropriate statistical analysis?
Q11. Was the response rate adequate?
Q12. If the response rate was inadequate, was the low response rate managed appropriately?

*Additional questions

3.3.5 Statistical analysis

Meta-analysis was executed in STATA version 13 (StataCorp LP) using "metaprop_one", a user-written command for meta-analysing proportions [16, 17]. Heterogeneity was quantified

using the I^2 measure [18]. Where heterogeneity was high (I^2 over 50%), no summary estimate was calculated.

It was possible to have multiple outcomes per study. Briefly, some studies reported multiple diagnostic methods for both pathogen and sequelae or multiple pathogen serotype/species. Each combination of pathogen diagnosis or sequelae diagnosis was considered as a separate outcome measure. Meta-analysis was performed using the most rigorous outcome measure based on the reference standard. For instance, where a study reported both laboratory-confirmed and probable diagnosis for a pathogen with multiple diagnostic methods for the sequelae of interest, such as self-reported diagnosis and further diagnosis by a specialist (Rheumatologist for reactive arthritis), the combination of *Campylobacter*/NTS cases with a laboratory-confirmed diagnosis and the sequelae assessed by a specialist was used.

A priori subgroups to explore potential sources of heterogeneity were investigated based on relevant methodological characteristics (study design, study size, follow-up period and sequelae diagnosis) [3, 9] and clinical characteristics (healthcare facility visited, symptoms of the selected GI infections, reported PPI or antibiotic usage) if data were available.

3.4 Results

Primary searches identified 4,133 references. On removal of duplicates and screening, five studies met the inclusion criteria reporting ReA, RS, IBS and GBS following *Campylobacter* infection (n=4) and ReA, RS and IBS following NTS infection (n=3) [19-23]. Data were extracted from all five studies and additional studies from the previous systematic reviews on ReA, RS, IBS and GBS following the selected GI infections (n =50). Hence 55 studies were included in the analysis (Figure 3-1 and Table 3-1). No eligible studies on IBD, CD and UC were

identified by the database search. Consequently, these sequelae are not considered further in this review.

Figure 3-1 Flowchart of included studies

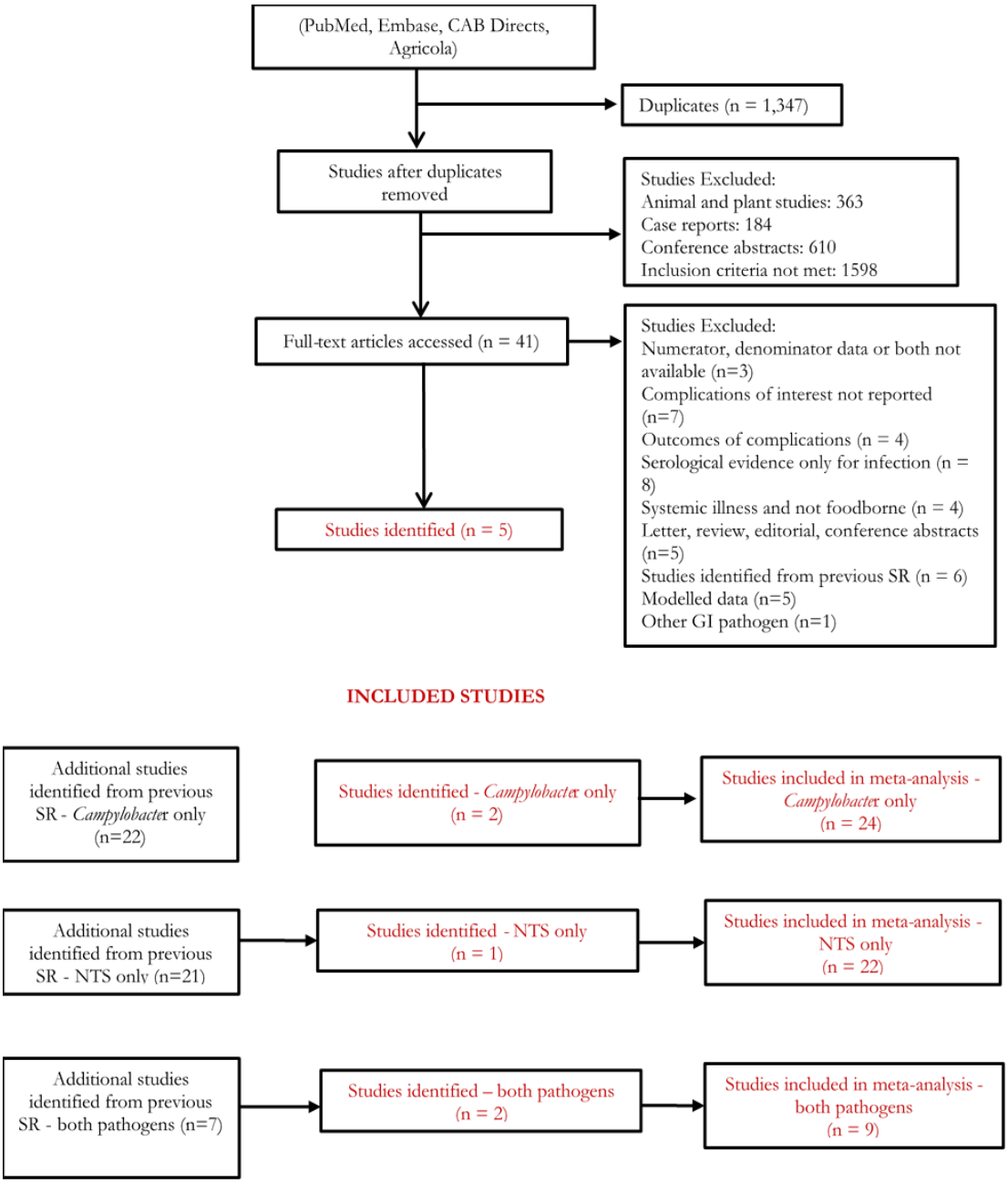


Figure 1 shows the results of all database searches, screening of titles and abstracts, full-text screening, additional references and selected studies

Table 3-1 Included studies by pathogen and sequelae reported

Sequelae	*Campylobacter*	NTS	*Campylobacter* & NTS
Reactive arthritis	(Gumpel, Martin, & Sanderson, 1981) [24], (Kosunen et al., 1981) [25], (Pitkanen, Pettersson, Ponka, & Kosunen, 1981) [26], (Short, Klouda, & Smith, 1982) [27], (C. Eastmond, Rennie, & Reid, 1983) [28], (Pitkanen, Ponka, Peterson, & Kosunen, 1983) [29], (Ponka, Pitkanen, Sarna, & Kosunen, 1984) [30], (Melby, Dahl, Crisp, & Penner, 1990) [31], (Bremell, Bjelle, & Svedhem, 1991) [32], (T Hannu et al., 2002) [33], (H Locht & Krogfelt, 2002) [34], (Schoenberg-Norio et al., 2010) [35] and (Uotila et al., 2014) [20]	(Hakansson, Eitrem, Low, & Winblad, 1976) [36], (C. J. Eastmond, 1983) [37] (Thomson, Chiu, De Rubeis, Falk, & Inman, 1992) [38], (H. Locht, Kihlstrom, & Lindstrom, 1993) [39], (Mattila, Leirisalo-Repo, Koskimies, Granfors, & Siitonen, 1994) [40], (Thomson, Alfa, Orr, Thomson, & Olson, 1994) [41], (Samuel et al., 1995) [42], (Mattila et al., 1998) [43], (Ekman, Kirveskari, & Granfors, 2000) [44], (McColl et al., 2000) [45], (Urfer et al., 2000) [46], (Dworkin, Shoemaker, Goldoft, & Kobayashi, 2001) [47], (Rudwaleit, Richter, Braun, & Sieper, 2001) [48], (Buxton, Fyfe, Berger, Cox, & Northcott, 2002) [49], (Hannu, Mattila, Siitonen, & Leirisalo-Repo, 2002) [50], (H. Locht, Molbak, & Krogfelt, 2002) [51], (Lee, Hall, & Pile, 2005) [52], (Rohekar et al., 2008) [53], (Arnedo-Pena et al., 2010) [54], and (Tuompo, Hannu, Mattila, Siitonen, & Leirisalo-Repo, 2013) [23]	(Petersen, Nielsen, Meyer, Ganer, & Ladefoged, 1996) [55], (Helms, Simonsen, & Molbak, 2006) [56], (Doorduyn et al., 2008) [57], (Schiellerup, Krogfelt, & Locht, 2008) [58], (Ternhag, Torner, Svensson, Ekdahl, & Giesecke, 2008) [59] and (Townes et al., 2008) [60]
Reiter's syndrome	None	(Thomson et al., 1994) [41], (Mattila et al., 1998) [43] and (Dworkin et al., 2001) [47]	(Doorduyn et al., 2008) [57] and (Porter, Choi, & Riddle, 2013) [21]
Irritable bowel syndrome	(Spiller et al., 2000) [61], (Thornley et al., 2001) [62], (Dunlop, Jenkins, Neal, & Spiller, 2003) [63] (Moss-Morris & Spence, 2006) [64], and (Spence & Moss-Morris, 2007) [65]	(McKendrick & Read, 1994) [66], (Urfer et al., 2000) [46] and (Mearin et al., 2005) [67]	(Helms et al., 2006) [56], (Saps et al., 2008) [68], (Ternhag et al., 2008) [59] and (Porter, Choi, Cash, et al., 2013) [22]
Guillain Barré Syndrome	(McCarthy, Andersson, Jormanainen, Gustavsson, & Giesecke, 1999) [69], (McCarthy & Giesecke, 2001) [70], (Helms et al., 2006) [56], (Tam et al., 2006) [71], (Ternhag et al., 2008) [59], (Doorduyn et al., 2008) [57], (Wang et al., 2008) [72], (Gardner et al., 2011) [73] and (Baker et al., 2012) [19]	None	None

3.4.1 Characteristics of included studies

Table 3-2 shows the characteristics of the included studies. The number of patients with the selected GI infections varied widely (range 6 to 57,425 with *Campylobacter* and 24 to 34,664

with NTS infection) and represented all age groups. Studies reported diagnoses of the pathogen and complication according to standard practices for all cases of the selected GI infections (87%, 48/55 and 75%, 41/55 respectively). Only 18% (10/55) reported adequate sample size calculation and, where the response rate was low (49%, 27/55), only 15% (n=4) adjusted for possible response bias in their analysis. Overall risk of bias score was not used as a criterion for selecting studies for a meta-analysis as it was possible to have a high score (>70%, 8.5/12) without using a reliable method of for detecting the GI pathogen and diagnosis of sequelae for all patients (Table 3-3).

Table 3-2 Study characteristics for complications following *Campylobacter* and non-typhoidal *Salmonella* infection

First Author, Year	Country	Study Design	Data Source	Outbreak Source	Date_Data Collection	Season	Age	% Female	Complication
				***Campylobacter* only**					
(Baker et al., 2012) [19]	New Zealand	Prospective population surveillance	Hospital records	N.A	1995-2008	All	All Ages	N.R	GBS
(Bremell et al., 1991) [32]	Sweden	Prospective outbreak	Outbreak in community	Unknown	1981	Autumn	Adults	56%	ReA
(Dunlop et al., 2003) [63]	England	Prospective population surveillance	Surveillance of population (sporadic or outbreak)	N.A	1999-2002	Various	Adult	N.R	IBS
(C. Eastmond et al., 1983) [28]	Scotland	Retrospective outbreak	Outbreak in community	Food - dairy	1979	Winter	N.R	N.R	ReA
(Gardner et al., 2011) [73]	Canada	Prospective outbreak	Outbreak in community	Food - vegetable	2008	Autumn	All Ages	51%	GBS
(Gumpel et al., 1981) [24]	England	Retrospective population surveillance	Surveillance of population (sporadic or outbreak)	N.A	1978	All	All Ages	N.R	ReA
(T Hannu et al., 2002) [33]	Finland	Prospective population surveillance	Surveillance of population (sporadic or outbreak)	N.A	1997-1998	All	All Ages	59%	ReA
(Kosunen et al., 1981) [25]	Finland	Unknown	Surveillance of population (sporadic or outbreak)	N.A	1978-1979	All	N.R	N.R	ReA
(H Locht & Krogfelt, 2002) [34]	Denmark	Retrospective population surveillance	Surveillance of population (sporadic or outbreak)	N.A	1997-2000	All	Adults	57%	ReA
(McCarthy et al., 1999) [69]	Sweden	Retrospective outbreak	Outbreak in community	Waterborne	1980, 1994, 1995	Various	N.R	N.R	GBS
(McCarthy & Giesecke, 2001) [70]	Sweden	Retrospective population surveillance	Disease registry	N.A	1987-1995	All	All Ages	N.R	GBS

First Author, Year	Country	Study Design	Data Source	Outbreak Source	Date_Data Collection	Season	Age	% Female	Complication
(Melby et al., 1990) [31]	Norway	Retrospective outbreak	Outbreak in community	Waterborne	Pre-1990	Spring/Summer	All Ages	48%	ReA
(Moss-Morris & Spence, 2006) [64]	New Zealand	Prospective population surveillance	Surveillance of population (sporadic or outbreak)	N.A	2002-2003	Various	Adults	N.R	IBS
(Pitkanen et al., 1983) [29]	Finland	Prospective hospital surveillance	Hospital records	N.A	1978-1981	All	All Ages	47%	ReA
(Pitkanen et al., 1981) [26]	Finland	Prospective hospital surveillance	Hospital records	N.A	1978-1980	All	All Ages	46%	ReA
Ponka et al., 1984) [30]	Finland	Prospective population surveillance	Surveillance of population (sporadic or outbreak)	N.A	1978-1981	All	N.R	N.R	ReA
(Schoenberg-Norio et al., 2010) [35]	Finland	Cross sectional	Surveillance of population (sporadic or outbreak)	N.A	2002	Summer	All Ages	48%	ReA
(Short et al., 1982) [27]	UK	Prospective	Hospital records	N.A	1979	Various	N.R	N.R	ReA
(Spence & Moss-Morris, 2007) [65]	New Zealand	Prospective	Surveillance of population (sporadic or outbreak)	N.A	Pre-2006	All	Adults	N.R	IBS
(Spiller et al., 2000) [61]	UK	Prospective population surveillance	Hospital records	N.A	Pre-2000	All	Adult	N.R	IBS
(Tam et al., 2006) [71]	UK	Retrospective population surveillance	Disease registry	N.A	1991-2001	All	N.R	N.R	GBS
(Thornley et al., 2001) [62]	UK	Prospective population surveillance	Surveillance of population (sporadic or outbreak)	N.A	1997	Spring/Summer	Adults	N.R	IBS
(Uotila et al., 2014) [20]	Finland	Retrospective outbreak	Outbreak in community	Waterborne	2007	Winter	All Ages	73%	ReA
(Wang et al., 2008) [72]	China	Retrospective population surveillance	Hospital records	N.A	2000-2006	All	Children	30%	GBS

First Author, Year	Country	Study Design	Data Source	Outbreak Source	Date_Data Collection	Season	Age	% Female	Complication
NTS only									
(Arnedo-Pena et al., 2010) [54]	Spain	Prospective outbreak	Outbreak in community	Food - meat	2005	Summer	All Ages	49.7%	ReA
(Buxton et al., 2002) [49]	Canada	Prospective population surveillance	Surveillance of population (sporadic or outbreak)	N.A	1999-2000	All	All Ages	53.0%	ReA
(Dworkin et al., 2001) [47]	USA	Prospective outbreak	Outbreak in community	Food - meat	1994	Autumn/Winter	Adults	58.5%	ReA, Reiter's
(C. J. Eastmond, 1983) [37]	Scotland	Prospective outbreak	Outbreak in community	Food - dairy	1981	Autumn	All Ages	47.8%	ReA
(Ekman et al., 2000) [44]	Finland	Prospective population surveillance	Surveillance of population (sporadic or outbreak)	N.A	1998-1999	All	NR	53.0%	ReA
(Hakansson et al., 1976) [36]	Sweden	Retrospective outbreak	Outbreak in community		1974	N.R	Adults	N.R	ReA
(T. Hannu et al., 2002) [50]	Finland	Prospective outbreak	Outbreak in community	Unknown	1999	Spring/Summer	Adults & Children	56.9%	ReA
(Lee et al., 2005) [52]	Australia	Retrospective outbreak	Outbreak in community	Food - vegetable	1999	Various	All Ages	48.3%	ReA
(H. Locht et al., 1993) [39]	Finland	Retrospective outbreak	Outbreak in community	Food- other	1990	Spring	Adults	44.4%	ReA
(H. Locht et al., 2002) [51]	Denmark	Prospective outbreak	Outbreak in community	Food- other	1999	Winter	Adults	56.0%	ReA
(Mattila et al., 1994) [40]	Finland	Prospective outbreak	Outbreak in community	Food - vegetable	1992	Autumn	All Ages	62.2%	ReA
(Mattila et al., 1998) [43]	Finland	Prospective outbreak	Outbreak in community	Food - vegetable	1994	Spring	All Ages	68.1%	ReA & Reiter's
(McColl et al., 2000) [45]	Australia	Prospective outbreak	Outbreak in community	Food - meat	1997	Spring	All Ages	51.0%	ReA
(McKendrick & Read, 1994) [66]	UK	Prospective outbreak	Outbreak in community	Food- other	Pre-1994	N.R	N.R	65.8%	IBS

First Author, Year	Country	Study Design	Data Source	Outbreak Source	Date_Data Collection	Season	Age	% Female	Complication
(Mearin et al., 2005) [67]	Spain	Prospective outbreak	Outbreak in community	Food - dairy	2002	Summer	Adults	55.3%	IBS
(Rohekar et al., 2008) [53]	Canada	Retrospective outbreak	Outbreak in community	Food - vegetable	2005	Autumn/Winter	Adults	71.2%	ReA
(Rudwaleit et al., 2001) [48]	Germany	Prospective outbreak	Outbreak in community	Food - dairy	1998	Winter	Children	N.R	ReA
(Samuel et al., 1995) [42]	USA	Retrospective outbreak	Outbreak in community	Unknown	1993	Summer	NR	N.R	ReA
(Thomson et al., 1994) [41]	Canada	Retrospective outbreak	Outbreak in community	Food - meat	1990	Spring	NR	N.R	ReA
(Thomson et al., 1992) [38]	Canada	Prospective outbreak	Outbreak in community	Food - meat	Pre-1992	N.R	Adults	94.5%	ReA
(Tuompo et al., 2013) [23]	Finland	Prospective population surveillance	Surveillance of population (sporadic or outbreak)	NA	2003-2004	Various	All Ages	60.1%	ReA
(Urfer et al., 2000) [46]	Switzerland	Prospective outbreak	Outbreak in community	Food - meat	1993	Autumn	All Ages	37.2%	IBS & ReA
***Campylobacter* and NTS**									
(Doorduyn et al., 2008) [57]	Netherlands	Prospective population surveillance	Surveillance of population (sporadic or outbreak)	N.A	2002-2003, 2005	All	NR	N.R	GBS, ReA, Reiter's
(Helms et al., 2006) [56]	Denmark	Retrospective population surveillance	Disease registry	N.A	1991-1999	All	All Ages	52%	GBS, IBS, ReA
(Petersen et al., 1996) [55]	Denmark	Retrospective hospital surveillance	Hospital records		1991-1993	All	All Ages	N.R	ReA
(Porter, Choi, & Riddle, 2013)[21]	USA	Retrospective population surveillance	Disease registry	N.A	1998 to 2009	All	Adults	N.R	Reiter's
(Porter, Choi, Cash, et al., 2013) [22]	USA	Retrospective population surveillance	Disease registry	N.A	1998 to 2009	All	Adults	N.R	IBS

First Author, Year	Country	Study Design	Data Source	Outbreak Source	Date_Data Collection	Season	Age	% Female	Complication
(Saps et al., 2008) [68]	USA & Italy	Prospective population surveillance	Hospital records	N.A	2006	Various	Children	N.R	IBS
(Schiellerup et al., 2008) [58]	Denmark	Prospective population surveillance	Surveillance of population (sporadic or outbreak)	N.A	2002-2003	All	Adults	57%	ReA
(Ternhag et al., 2008) [59]	Sweden	Retrospective population surveillance	Surveillance of population (sporadic or outbreak)	N.A	1997-2004	All	All Ages	*Campylobacter* - 47% NTS - 50.6%	GBS, IBS, ReA
(Townes et al., 2008) [60]	USA	Prospective population surveillance	Surveillance of population (sporadic or outbreak)	N.A	2002-2004	All	All Ages	*Campylobacter* - 46.9% NTS - 56.0%	ReA

N.A – Not Applicable; N.R – Not Reported

Table 3-3 The Joanna Briggs Institute Prevalence Critical Appraisal Tool (adapted)

Author & Year	Q1	Q2	Q3	Q4	Q5	Q6*	Q7	Q8*	Q9	Q10	Q11	Q12
Arnedo-Pena 2010[54]												
Baker 2012[19]												
Bremell 1991[32]												
Buxton 2002[49]												
Doorduyn 2008[57]												
Dunlop 2003[63]												
Dworkin 2001[47]												
EastmondA 1983[74]												
EastmondB 1983[37]												
Ekman 2000[44]												
Gardner 2011[73]												
Gumpel 1981[24]												
Hakansson 1976[36]												
HannuA 2002[33]												
HannuB 2002[50]												
Helms 2006[56]												
Kosunen 1981[25]												
Lee 2005[52]												
Locht 1993[39]												
LochtA 2002[34]												
LochtB 2002[51]												
Mattila 1994[40]												
Mattila 1998[43]												
McCarthy 1999[69]												

Author & Year	Q1	Q2	Q3	Q4	Q5	Q6*	Q7	Q8*	Q9	Q10	Q11	Q12
McCarthy 2001[70]												
McColl 2000[45]												
McKendrick 1994[66]												
Mearin 2005[67]												
Melby 1990[31]												
Moss-Morris 2006[64]												
Petersen 1996[55]												
Pitkanen 1981[26]												
Pitkanen 1983[29]												
Ponka 1984[30]												
PorterA 2013[21]												
PorterB 2013[21]												
Rohekar 2008[53]												
Rudwaleit 2001[48]												
Samuel 1995[42]												
Saps 2008[68]												
Schiellerup 2008[75]												
Schonberg-Norio 2010[76]												
Short 1982[27]												
Spence 2007[65]												
Spiller 2000[61]												
Tam 2006[71]												
Ternhag 2008[59]												
Thomson 1992[38]												
Thomson 1994[41]												

Author & Year	Q1	Q2	Q3	Q4	Q5	Q6*	Q7	Q8*	Q9	Q10	Q11	Q12
Thornley 2001[62]												
Townes 2008[60]												
Tuompo 2013[23]												
Uotila 2014[20]												
Urfer 2000[46]												
Wang 2007[72]												
Total number of studies with "Yes"	41	51	10	43	42	48	41	42	32	45	27	4

*The questions were repeated for the pathogen and sequelae as an adaptation to the tool.

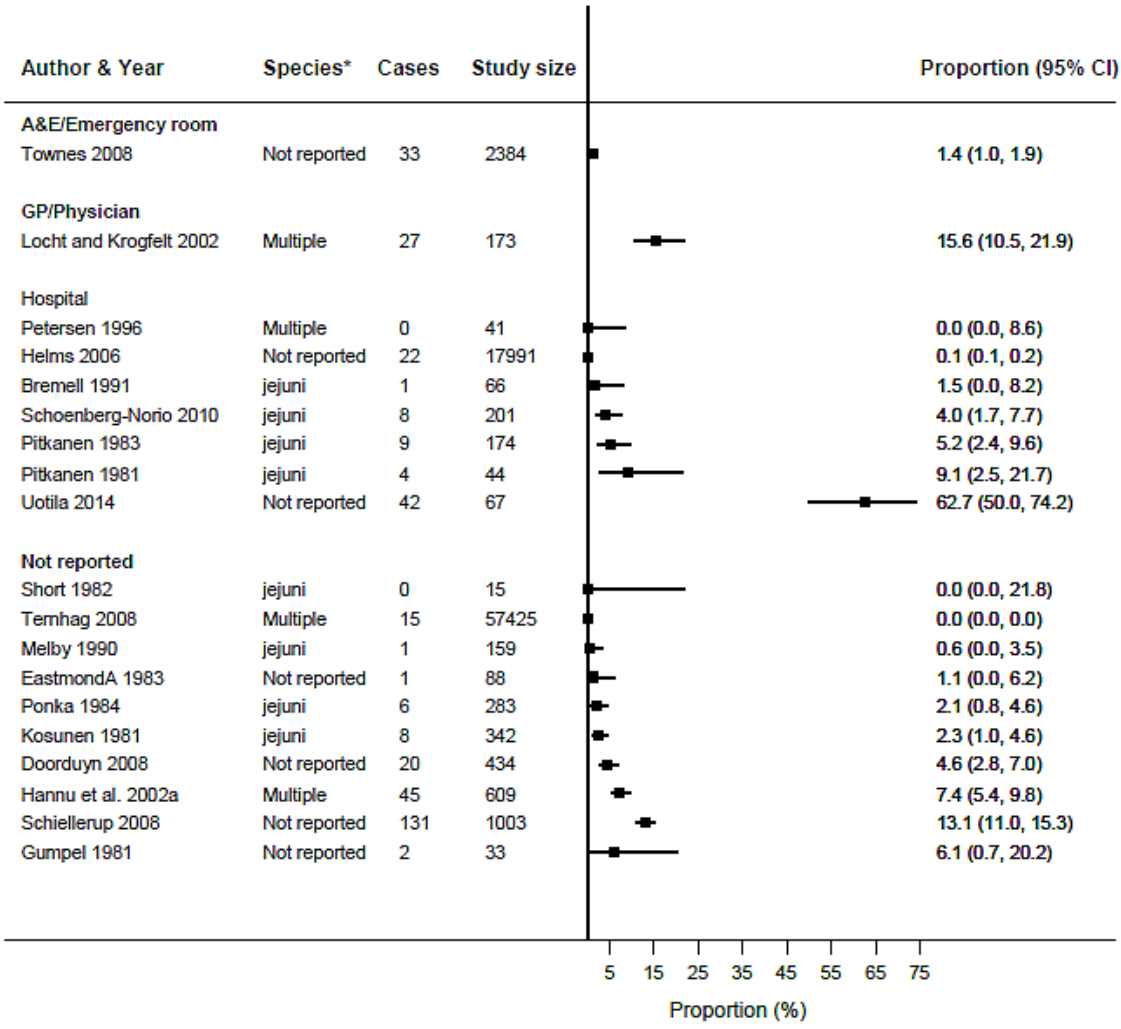
No
Unclear
Yes

The risk of bias tool is an adapted version of the Joanna Briggs Critical Appraisal Tool. Total score per paper was not assigned. The full questions are listed in section 3.3.4 (page 28).

3.4.2 The proportion of patients developing sequelae

Thirty-seven studies reported ReA following *Campylobacter* (n = 19) and NTS infections (n = 26) [20, 23, 24, 26-54, 56-59, 77, 78] in up to 63% of patients with either infection (Appendix 3-3). Most studies reported ReA triggered by *Campylobacter* (n = 14) or NTS infection (n =18) in less than 10% of patients with gastroenteritis. No overall summary of the incidence of sequelae following gastroenteritis was calculated, as there was a high level of heterogeneity across studies (I^2>90%) (Figures 3-2 to 3-3). The incidences of RS and IBS were reported in 5 and 12 studies, respectively (Figures 3-4 to 3-6). Less than 10% of patients with either infection developed RS in all studies. Incidence of IBS was reported in *Campylobacter* (0% to 18%) and NTS (0% to 38%) patients. GBS, reported by nine studies was less frequent with all but one study reporting an incidence of less than 2% following *Campylobacter* infection (Figure 3-7).

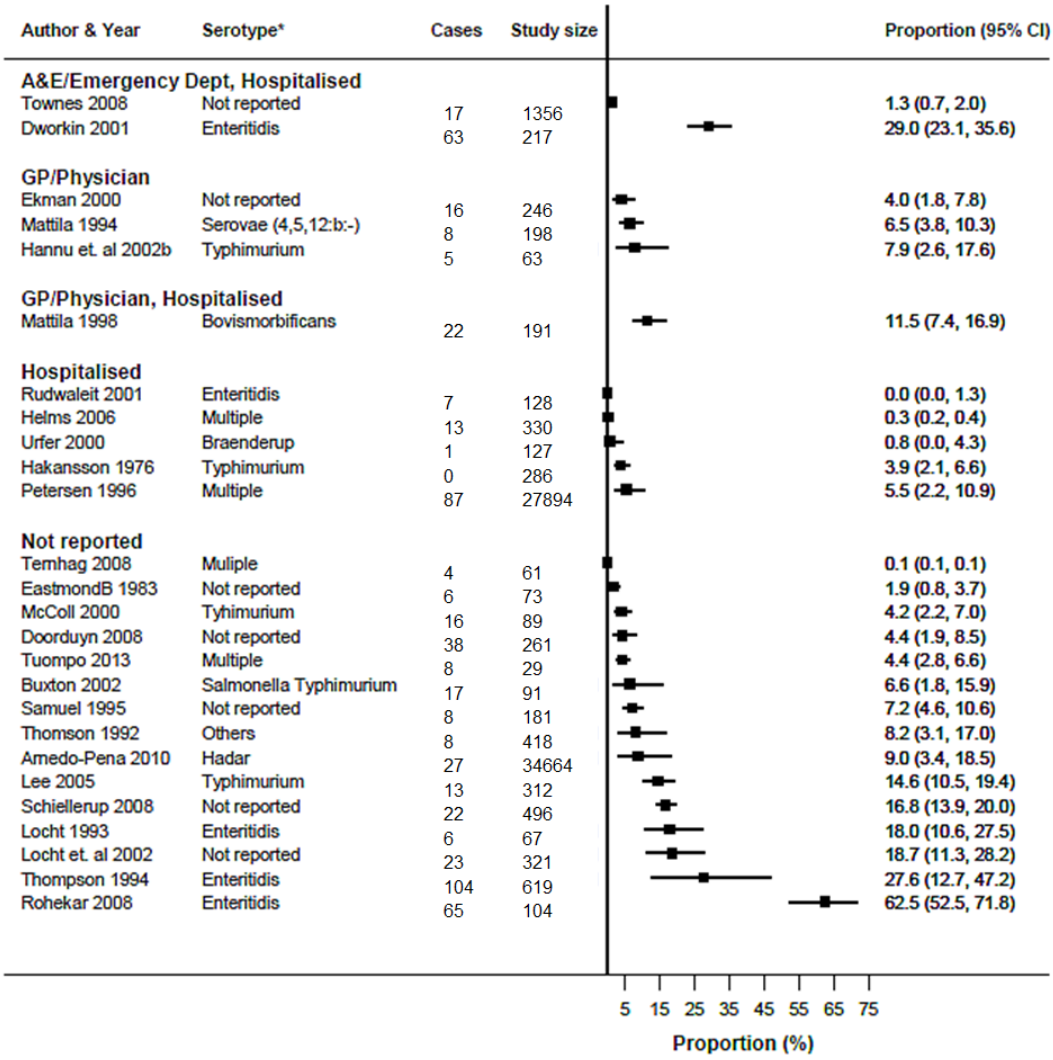
Figure 3-2 Forest plot of studies reporting the incidence of *Campylobacter* triggered ReA stratified by the healthcare facility visited



(Permission to reproduce this figure has been granted by Elsevier B.V)

Studies reporting the incidence of reactive arthritis following *Campylobacter* infection stratified by the type of healthcare facility/practitioner visited/utilised. No summary estimate was calculated due to high heterogeneity across all studies (I^2 >90%). Species*: Multiple - *Campylobacter jejuni, Campylobacter coli, Campylobacter spp.* and undetermined

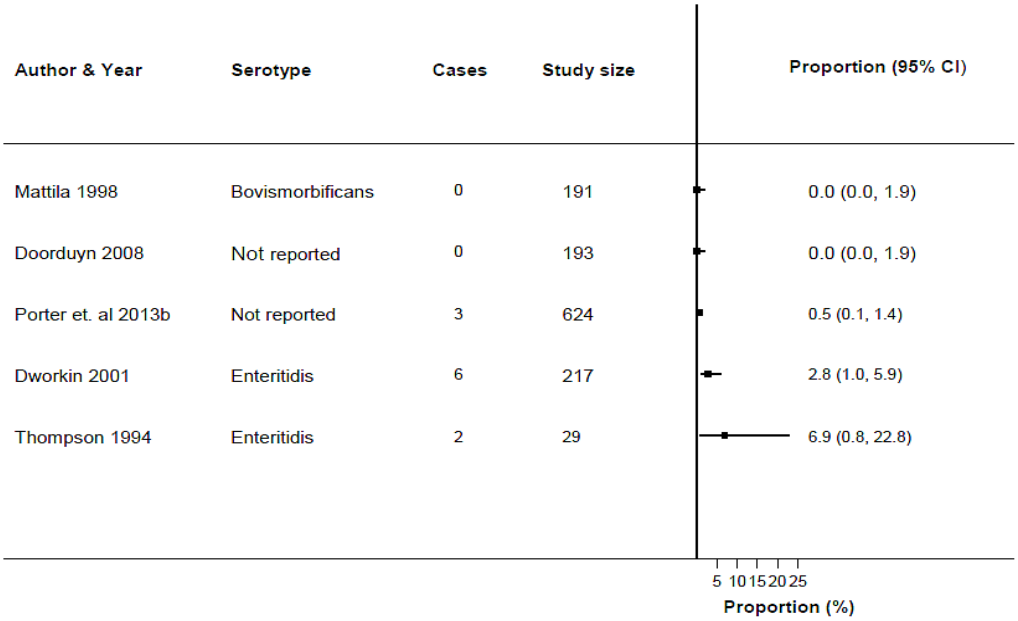
Figure 3-3 Forest plot of studies reporting the incidence of NTS triggered ReA stratified by the healthcare facility visited



(Permission to reproduce this figure has been granted by Elsevier B.V)

Studies reporting the incidence of reactive arthritis following non-typhoidal *Salmonella* infection stratified by the type of healthcare facility/practitioner visited/utilised. No summary estimate was calculated due to high heterogeneity across all studies (I^2 >90%).

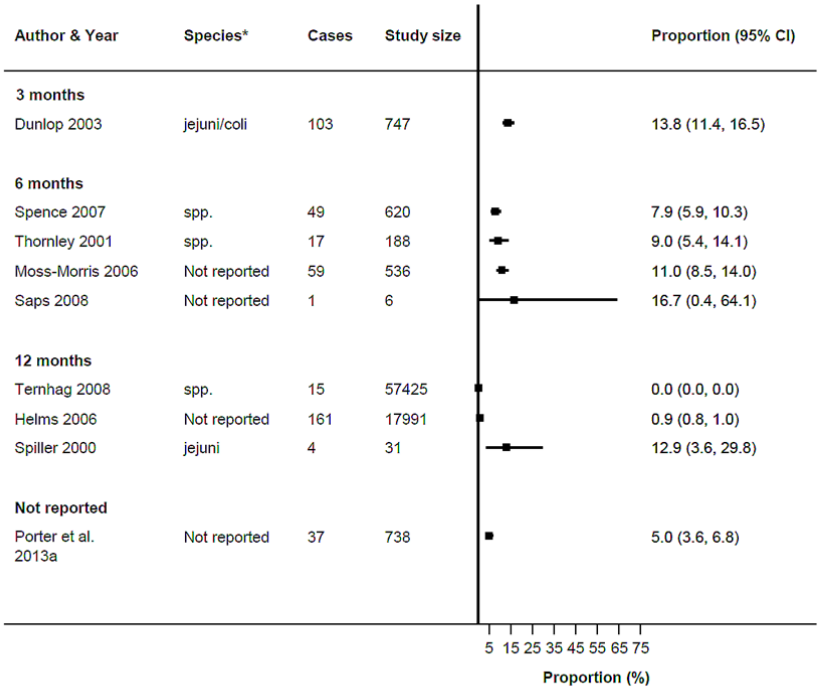
Figure 3-4 Forest plot of studies reporting the incidence of RS following NTS infection



(Permission to reproduce this figure has been granted by Elsevier B.V)

Studies reporting the incidence of Reiter's syndrome following non-typhoidal *Salmonella* infection. No summary estimate was calculated due to high heterogeneity across all studies (I^2 >90%).

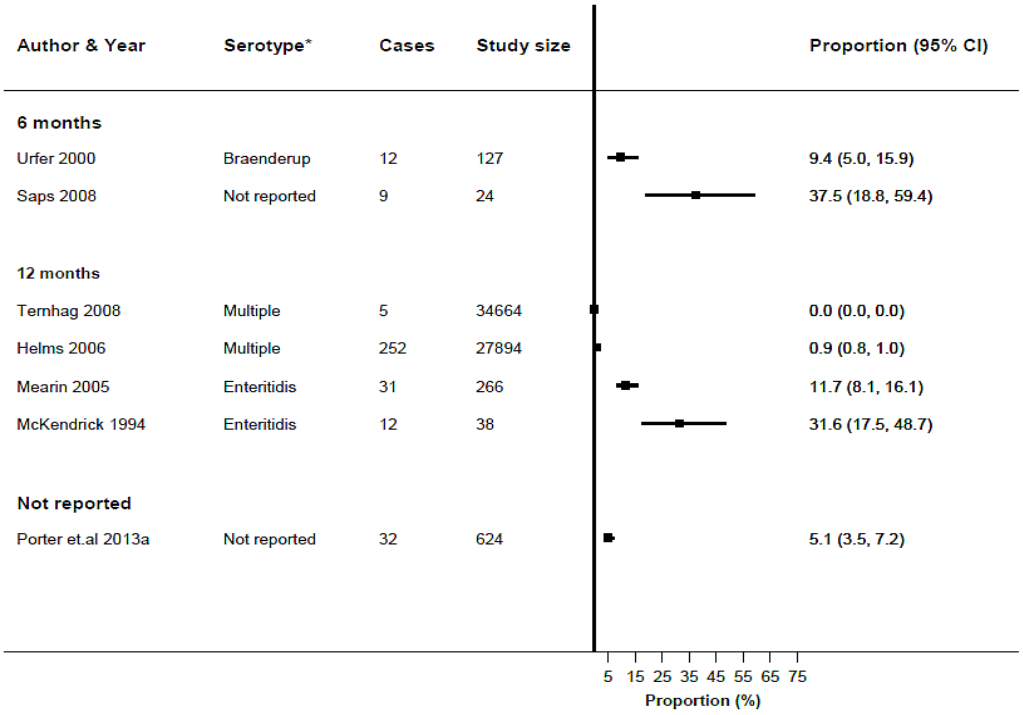
Figure 3-5 Forest plot of studies reporting the incidence of IBS following Campylobacter infection stratified by follow-up period



(Permission to reproduce this figure has been granted by Elsevier B.V)

Studies reporting the incidence of irritable bowel syndrome following *Campylobacter* infection stratified by the length of follow-up from infection to sequelae. No summary estimate was calculated due to high heterogeneity across all studies (I^2 >90%).

Figure 3-6 Forest plot of studies reporting the incidence of IBS following NTS infection stratified by follow-up period



(Permission to reproduce this figure has been granted by Elsevier B.V)

Studies reporting the incidence of irritable bowel syndrome following non-typhoidal *Salmonella* infection stratified by the length of follow-up from infection to sequelae. No summary estimate was calculated due to high heterogeneity across all studies (I^2 >90%). Serotype*- Multiple (Typhimurium, Enteritidis and other NTS), Others (other NTS excluding Typhimurium and Enteritidis)

3.4.3 Factors associated with the onset of sequelae

Only studies reporting the incidence of ReA considered the use of PPI or antibiotics as potential factors contributing to sequelae development. One study assessing the long-term use of PPI in the development of ReA following *Campylobacter* and NTS infection found a significant association after adjustment for age, sex and degree of urbanisation (adjusted OR 2.9 (95% CI 1.4-6.1)) [57]

The prescription/usage of antibiotics was reported in 17 studies (n = 7 for *Campylobacter* and n = 11 for NTS)[20, 23, 26, 29, 30, 34, 39, 43, 44, 47-50, 52, 54, 60, 76]. Seven studies considered the risk of ReA

development following antibiotics usage [34, 43, 47, 49, 50, 54, 60]. Of these studies, increased risk of ReA development was observed following treatment of infection with antibiotics (class not provided) for *Campylobacter* and fluoroquinolones for NTS infection (n = 1 and 2, respectively)[34, 43, 47]. Three studies found a protective effect in the use of antibiotics for NTS; however, the findings were not statistically significant [49, 50, 54]. The remaining study did not find any associated risk with antibiotic usage for either *Campylobacter* or NTS infection. Moreover, the data was not reported in the study (Table 3-4) [60]. Studies assessing the association of antibiotic treatment and development of ReA reported a visit to a GP/Physician (n=4) or accident and emergency/hospital (n =3).

Clinical symptoms were scarcely reported by studies and, where available, studies used different definitions and thresholds for diarrhoea and fever (data not shown). This prevented further analysis of the role of symptom severity in sequelae development.

For the methodological subgroup analysis, only consultation with a rheumatologist statistically reduced the heterogeneity of studies within the "specialist" stratum in *Campylobacter* and NTS triggered ReA (Table 3-5, Figures 3-2 and 3-3). Follow-up may have contributed to heterogeneity in *Campylobacter* triggered IBS as studies within the 6-month follow-up stratum had a statistically significant reduction in heterogeneity (I^2=24.2%) (Table 3-5, Figure 3-6). The only clinical characteristic considered in a subgroup analysis was the healthcare facility visited for the GI infection in those developing ReA and IBS. Studies reporting a "GP/Physician" visit for NTS infection were relatively homogenous (I^2= 2.0%), nonetheless high heterogeneity remained in this stratum for patients with *Campylobacter* triggered ReA (Figures 3-2 and 3-3).

Table 3-4 Risk of developing ReA following prescription/usage of antibiotics in Campylobacter and NTS patients stratified by healthcare facility accessed

Author_Year	Pathogen	No. with pathogen	Antibiotics usage N (%)	Antibiotics	Proportion of ReA vs Non-ReA using antibiotics
Visited General Practitioner/Physician					
(H Locht & Krogfelt, 2002) [34]	*Campylobacter*	173	56 (32)	N.R	56% with ReA vs. 26% non-ReA; p=0.03*‡
(Arnedo-Pena et al., 2010) [54]	*S*. Hadar PT2	155	57 (38) &	Fluoroquinolones	aRR† 0.43; 95% C.I 0.17-1.08
(T. Hannu et al., 2002) [50]	*S*. Typhimurium DT193	63	32 (63)&	Fluoroquinolones	0% with ReA vs. 16% no ReA; p=0.056
(Mattila et al., 1998) [43]	*S*. Bovismorbificans	191	78 (41)	Fluoroquinolones	59% with ReA vs. 35% non-ReA; p=0.021*‡
Visited accident&emergency/hospitalised					
(Dworkin, Shoemaker, Goldoft, & Kobayashi, 2001) [47]	*S*.Enteritidis	217	66 (30)	Fluoroquinolones	RR 1.6; 95% C.I 1.1-2.5*
(Townes et al., 2008) [60]	NTS	1356	365 (27)	Quinolone, B-lactam and Macrolide	No associated risk (data not reported)
(Townes et al., 2008) [60]	*Campylobacter*	2384	1978 (83)	Quinolone, B-lactam and Macrolide	No associated risk (data not reported)
Visit of healthcare facility not reported					
(Buxton, Fyfe, Berger, Cox, & Northcott, 2002) [49]	*S*.Typhimurium	61	28 (46)	N.R	OR 0.29; 95% C.I 0.07-1.18

*Significant results; &Antibiotics information not available for all with gastroenteritis; †adjusted Relative Risk; ‡Chi-squared test in comparison of the proportion

Table 3-5a Subgroup meta-analysis for studies reporting the development of reactive arthritis following *Campylobacter* infection by sequelae diagnosis, follow-up period, study size and healthcare facility visited

Variable	I^2	Number of studies
Sequelae diagnosis		
Physician/Medical Records	95.6%	6
Self-reported disease status	97.0%	6
Self-reported disease status based on a validated scale	-	1
Specialist*	48.6%	2
Combination	0.0%	3
Not reported	-	1
Follow-up period		
< 3 months	97.0%	8
3 months	-	1
> 3 months < 1 year	-	-
1 year	95.6%	3
> 1 year	97.8%	2
Not reported	56.4%	5
Study size		
Extra small (n < 100)	95.3%	7
Small (101 -500)	86.3%	7
Medium (501-1,000)	-	1
Large (1,001 -10,000)	97.70%	2
Extra-large (> 10,000)	99.20%	2
Healthcare facility visited		
GP/Physician	-	1
GP/Hospitalised	-	-
A&E/Hospitalised	-	1
Hospitalised	97.8%	7
Not reported	98.8%	10

*heterogeneity significantly reduced (I^2 < 50%)

Table 3-5b Subgroup meta-analysis for studies reporting the development of reactive arthritis following NTS infection by sequelae diagnosis, follow-up period, study size and healthcare facility visited

Variable	I^2	Number of studies
Sequelae diagnosis		
Physician/Medical Records	97.7%	9
Self-reported disease status	96.8%	9
Self-reported disease status based on a validated scale	-	1
Specialist*	41.2%	6
Combination	-	1
Not reported	-	1
Follow-up period		
< 3 months	97.3%	10
3 months	81.3%	5
> 3 months < 1 year	93.5%	4
1 year	97.8%	2
> 1 year	95.3%	2
Not reported	97.7%	4
Study size		
Extra small (n < 100)	58.8%	7
Small (101 -500)	95.6%	16
Medium (501-1,000)	96.1%	1
Large (1,001 -10,000)	-	1
Extra-large (> 10,000)	99.80%	1
Healthcare facility visited		
GP/Physician*	2.0%	3
GP/Hospitalised	-	1
A&E/Hospitalised	99.9%	2
Hospitalised	91.7%	5
Not reported	98.8%	20

*heterogeneity significantly reduced (I^2 < 50%)

Table 3-5c Subgroup meta-analysis for studies reporting the development of irritable bowel syndrome following *Campylobacter* infection by sequelae diagnosis, follow-up period, study size and healthcare facility visited

Variable	I^2	Number of studies
Sequelae diagnosis		
Physician/Medical Records	99.6%	3
Self-reported disease status based on a validated scale	63.2%	6
Follow-up period		
3 months	-	1
> 3 months < 1 year*	24.2%	4
1 year	99.4%	3
Not reported	-	1
Study size		
Extra small (n < 100)	87.7%	3
Small (101 -500)	-	1
Medium (501-1,000)	92.2%	4
Extra large (> 10,000)	99.90%	2

*heterogeneity significantly reduced (I^2 < 50%)

Table 3-5d Subgroup meta-analysis for studies reporting the development of irritable bowel syndrome following NTS infection by sequelae diagnosis, follow-up period, study size and healthcare facility visited

Variable	I^2	Number of studies
Sequelae diagnosis		
Physician/Medical Records	99.6%	3
Self-reported disease status	-	1
Self-reported disease status based on a validated scale	87.3%	3
Follow-up period		
> 3 months < 1 year	99.8%	2
1 year	99.5%	4
Not reported	-	1
Study size		
Extra small (n < 100)	87.7%	3
Small (101 -500)	-	1
Medium (501-1,000)	-	1
Extra-large (> 10,000)	99.20%	2
Healthcare facility		
Hospitalised	99.70%	2
Not reported	98.8%	5

3.5 Discussion

The use of PPI or antibiotics may be modifiable risk factors associated with the development of ReA following *Campylobacter* and NTS infections. These factors were sparsely reported by studies, and where information was available high heterogeneity (I^2 >90%) prevented the pooling of data. Previous systematic reviews considering the incidence of ReA, RS, IBS and GBS conducted literature searches up until 2011 without assessing factors contributing to sequelae development. Five years after these searches were conducted, only five studies were identified based on the inclusion criteria.

Despite the over-prescription of PPI in both primary and secondary settings, only one study reported an association of PPI usage and ReA development in patients with gastroenteritis [57, 79]. PPI usage was independent of a single nucleotide polymorphism (SNP) in interferon gamma (IFN-ɣ) in cases with *Campylobacter* and NTS infections and the development of ReA in the study [57]. IFN-ɣ is a cytokine crucial in the immune response against enteric infections. The combination of an SNP in IFN-ɣ with PPI usage could lead to increased susceptibility to enteric infections and subsequent prolonged or repeated episodes of these GI infections. These sequential events may increase the susceptibility to ReA [57].

Of all the sequelae considered, only the risk of ReA was assessed following antibiotic usage in cases of *Campylobacter* and NTS infection. The associated risk is not clear as the studies report elevated, decreased, or no risk of ReA following these GI infections. The association may be dependent on the dose and type of antibiotics, as evidenced in a systematic review evaluating the risk of HUS following the use of antibiotics in patients with STEC infections [80]. Agger et al. (2015) demonstrated that protein and cell wall synthesis class of antibiotics might be protective and improve recovery time based on population and in-vitro studies.

Most cases of gastroenteritis do not require treatment with antibiotics unless they are severe and occur in at-risk groups, i.e. older people, children and those with underlying comorbidities. Due to insufficient information in the studies, it was not possible to assess the potential reason for antibiotic treatment or the risk associated with sequelae development following antibiotic usage in a meta-analysis. Moreover, information on the duration of treatment, the dose of antibiotics, age and gender of all cases who received antimicrobial treatment were not available for all of the studies, precluding any further comparisons or pooling of data.

Heterogeneity could not be explained by most of the subgroup analysis considered, except in the reported method of diagnosing ReA complication following *Campylobacter* and NTS infection, the type of healthcare facility visited for an NTS infection and follow-up period in *Campylobacter*

triggered IBS. In studies reporting a visit to the GP/Physicians amongst patients with NTS infection, the heterogeneity was significantly reduced (I^2 = 2%). The three studies were all conducted in Finland, reported specialist diagnosis for ReA, had laboratory confirmation of the NTS infection, and two assessed the use of antibiotics in development of ReA. A GP/Physician consultation may lead to a laboratory-confirmed diagnosis of infection, prescription of antibiotics, and referral to a specialist; hence influencing the reported sequelae incidence. The small number of studies with inconsistent follow-up period from NTS infection to ReA development limits the further interpretation of this finding.

Follow-up period may be crucial in the reported incidence of IBS following campylobacteriosis, due to a statistically significant reduction in heterogeneity in studies reporting a 6-month follow-up period, despite using different versions of Rome I, II and III criteria for diagnosis. The gold-standard for IBS diagnosis is the Rome III classification. Introduced in 2006, it is symptom-based, requiring patients to be symptomatic both at 3 and 6 months after initial onset [81]. Only one study used this approach [65]. Following the conduct of this review a new version of the Rome criteria, Rome IV was introduced in 2016, with the main difference being the removal of the term "discomfort in the definition and diagnostic criteria because some languages do not have a word for discomfort and it has different meanings in different languages [59]. Potential risk-modifying factors in the development of IBS following gastroenteritis were not evaluated due to insufficient reporting and the primary aim of included studies.

The data source may be a potential source of unexplained heterogeneity even though it was not significant in the subgroup analysis (data not shown). Using a combination of study types with source population drawn from outbreaks, population surveillance and hospital surveillance may have introduced additional heterogeneity. Outbreaks are usually caused by a single strain, while population surveillance identifies the circulating strains. In one of the studies included in this review, Tuompo et al. (2013) used phenotypic methods to determine potential differences in the

O-antigens of different NTS serotypes circulating in population surveillance. However, no significant differences in the arthritogenicity of the serotypes to trigger ReA were identified [23]. The precision of genomic methods, such as whole genome sequencing, may provide further insights into the differing potential for bacterial strains to trigger sequelae.

3.5.1 Strengths and limitations

Strengths

This is the first systematic review to assess the available evidence on factors contributing to the development of sequelae following *Campylobacter* and NTS infection. This is important in understanding factors amenable to intervention. The review highlights the need for investigators to consider remediable risk factors in sequelae development following these GI infections.

Limitations

The reliance on observational studies on "natural experiments" such as outbreaks makes them prone to low study quality and high level of bias and heterogeneity. Most outbreak investigations are set up as a rapid response to an emergency to determine the cause of the outbreak. Time constraints in these investigations limit the opportunity to address secondary factors that may improve the overall evidence on *Campylobacter* or NTS triggered sequelae. Therefore, it was possible for a study to have a high-quality score for the primary research but missing key items such as the method of diagnosis of pathogen and sequelae, crucial for risk factor study. Hence, a quality criterion was not adopted for the inclusion of studies for meta-analyses. Although heterogeneity was significantly reduced for studies reporting a specialist consultation for diagnosis of ReA following either *Campylobacter* or NTS infection, I did not report a pooled estimate. The specialist diagnosis was preceded by self-reported symptoms. Not all patients with symptoms were seen by a specialist. Further, the studies reported different follow-up times indicating different definitions of ReA were adopted.

Other limitations of the study include inconsistencies in the reporting of key features, such as age, the definition of sequelae, and follow-up of gastroenteritis cases in included studies. The risk factors considered were also sparsely reported. Further, unexplained sources of heterogeneity prevented the reporting of a summary statistic for factors contributing to sequelae development. These limits the application of estimates to the general population and made interpretation of results difficult.

3.5.2 Implications of findings for the thesis

The findings of this systematic review show the paucity of studies assessing the factors contributing to sequelae of *Campylobacter* and NTS infections, and where this was reported, the evidence was inconclusive. This highlights the need to address the gap.

There is a dearth of publication on sequelae of *Campylobacter* and NTS infections in the UK. The most recent on ReA was published in 1983, IBS in 2001, and GBS in 2006. This may have been due to the lack of adequate data sources.

Record linkage of a patient's health journey can overcome these issues in providing recent estimates of sequelae of these GI infections. Using routinely collected observational data validated for research such as CPRD will provide up to estimates on sequelae in England. The availability of information on potential risk modifiers in CPRD will allow the quantification of the risks in the onset of sequelae, with individual patient-level data allowing further stratification of patient's demographic and clinical characteristics.

3.6 References

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Chapter 4

Methodology and research tools

4.1 Overview

In this chapter, the data sources including their strengths and limitations are described, followed by the required ethical approvals for all the studies and the presentation of the overall study design. The steps adopted to prepare data for analyses are outlined with specific details on the epidemiological concepts, statistical terms and methods applicable to the objectives B, C, and D. The results are presented in Chapters 5, 6, and 7.

4.2 Data sources

The ideal data source should represent the source population from where it is drawn, contain information on the exposure and outcome variables, and adequate historical records to measure baseline covariates. Hence, the data choice is driven by the research question. For this thesis, the questions did not warrant the primary collection of data through a randomised clinical trial, as existing databases were adequate. These observational data include primary and secondary care EHR and administrative data. The EHR and administrative data used varied in population, availability of denominator data, timeliness, accuracy, precision and completeness owing to their nature as secondary sources of data not primarily collected for the research questions in this thesis. However, the linkage of individual patient records makes the population consistent.

4.2.1 Clinical Practice Research Datalink

Overview of dataset

The main data source utilised was the Clinical Practice Research Datalink (CPRD). It is one of the world's largest longitudinal database of primary care records. It was originally created in 1987 through an incentive scheme where participating General Practices in England were provided with free computing equipment in return for recording standardised patient-level data into a central database for research by the Value Added Medical Products Ltd software company [1,2]. It later evolved into the General Practice Research Database (GPRD) in 1993 following the transfer of the database to the UK Department of Health and Social Care (DHSC) [2]. On further expansion and transfer of ownership and management to the Medicines and Healthcare products Regulatory Agency (MHRA) in 2012, the CPRD was established in its present form [3]. As of December 2014, the database contained records on 13.6 million research usable patients from 684 participating general practices from all regions of the UK at a coverage of 6.9% of the population [3].

CPRD collects the entire medical record of patients from participating practices unless patients have opted out. Only anonymised data without strong patient identifiers (e.g. name, address, date of birth, NHS number and post-code) are available to the end user. Information collected includes demographic information (including age and sex), medical symptoms, signs and diagnoses, therapy, referrals to hospitals or specialists, laboratory tests and pathology results, lifestyle factors (e.g. height, weight, body mass index (BMI), smoking and alcohol consumption) and patient registration details [3]. The completeness of the data may vary from practice to practice, as General Practitioners (GPs) primarily use the electronic records for managing patients, as opposed to recording information for research purposes. For this reason, CPRD routinely performs quality checks on participating practices and their patients' records using a data quality marker known as "up-to-standard" (UTS) time for practise and "acceptability" for patients. The UTS date is calculated for each participating practice and corresponds to the latest date at which practices meet

the minimum quality criteria for the continuity of recording and the number of recorded deaths. While the acceptability patient quality metric is based on the registration status, recording of events in the patient record, and valid age and sex [3].

Clinical data within the dataset are coded using 'Read' codes, developed by Dr James Read in 1982, and based on the 9th version of the International Classification of Diseases (ICD) codes [4]. They follow a hierarchical structure and enable GPs to record more specific diagnoses than were previously possible with the former Oxford Medical Information Systems (OXMIS) codes. Read codes replaced OXMIS codes in 1995, following instruction from the DHSC for their use in electronic diagnostic classification in general practice. The data analysed in this thesis are from 2000 onwards and thus only used Read codes. The CPRD provides lists of diagnostic codes (CPRD medical codes), which are mapped from Read codes. The selection of patients was defined by the CPRD medical codes for the consultations of GI infections of interest. Likewise, relevant exposures and outcomes of interest were also selected based on the CPRD medical codes. The potential exposures were selected based on the existing literature of potential risk factors and the data available within the CPRD.

Strengths and weaknesses of CPRD

The age and sex distribution of CPRD is broadly representative of the UK population and validation studies have shown a high positive predictive value for different disease categories [3,5]. Incidence estimates with other disease registries are also comparable. The incidence of tuberculosis amongst CPRD patients in comparison and the proportion of gastrointestinal infection attributable to norovirus within primary care were both comparable to data held by PHE [6,7].

There are potential limitations inherent to the CPRD database. Similar to other disease registers, misclassification of diagnoses can occur. In infectious diseases, laboratory confirmation is the gold standard in differentiating between viral, bacterial and parasitic infections. For common acute infections which are self-limiting in most patients such as gastroenteritis, laboratory requests for

stool culture vary amongst GPs despite clear guidelines on when and how to request stool specimens from patients [8,9].

Lack of standardised definitions for diseases can also be a hindrance. Individual studies usually develop Read code lists and algorithms to identify exposures and outcomes of interest. For instance, some studies investigating GI infections using CPRD use all Read codes indicating gastroenteritis regardless of known causative pathogen and only differentiate between infectious and non- infectious causes [10]. Others extend this further by applying a regression model to attribute different causative pathogens [7]. These inconsistencies in definitions limit comparisons between studies [3].

The CPRD data collected is not recorded for research and hence completeness of data between patients and over time may vary (for different variables for different reasons). For example, changes in ethnicity classification following the 2011 census led to improved recording, although overall completeness is still low [3,11,12].

Other primary care databases

Other existing primary care databases include QResearch, and The Health Improvement Network (THIN). QResearch comprises a sample of around 1,500 General Practices across the UK that use Egton Medical Information Systems (EMIS) clinical software [13]. Although EMIS is the leading primary care information technology provider in the UK, only a minority of practices in Scotland and Northern Ireland use it [14]. Similar to CPRD, the data can also be linked to HES and ONS data. However, this is only limited to researchers at the hosting institution, which was previously the University of Nottingham since its inception in 2003 up until 2019, where the University of Oxford became the hosting institution [13]. Further, bespoke linkage to other datasets is currently not possible as patients' identifiers are not available. Data is extracted based on Read codes on clinical consultations, prescriptions, tests and results, and referrals for a population of approximately 35 million patients currently registered, making it the largest of the three databases.

The THIN database is a collaboration between In Practice Systems (INPS) and Cegedim Healthcare Software, hence data is exclusively from the Vision/INPS software [15]. THIN is profit-making and can be used by pharmaceutical companies for commercial purposes. It is the smallest of all three databases consisting of 12 million patients from around 600 practices [14].

CPRD, QResearch and THIN vary slightly in the quality of the data due to the type of software used in harnessing data. Data contained within CPRD have historically been derived mainly from Vision/INPS. However, any General Practice can contribute data after a data sharing agreement with the software supplier. Thus it is not limited to data extracted from a clinical propriety system, and it is the only one available online [2]. Vision/INPS is a Problem Oriented Medical Record (POMR) software, as such, the linkage of medical and drug information or consultations to a specific coded problem(s) is mandated [15]. EMIS, however, is an Episode Oriented Medical Record (EOMR) software, meaning that this linkage is not obligated [15]. POMR-based systems reduce intra-patient coding variability, thereby improving data quality [15]. However, the impact of this is thought to be minimal as all three databases use Read codes [16]. Further, validation studies comparing risk prediction models using CPRD and QResearch show that differences in population characteristics, data definitions, recording, quality and completeness had a minimal impact on key statistical outputs [17] [16].

Of relevance to infectious diseases is the Royal College of General Practitioners (RCGP) Sentinel Surveillance data .[1,18] This primary care data resource is on a smaller scale in terms of coverage, with over 1.7 million patients, which equates to approximately 3.1% of England's population [18]. However, the use of this data for routine surveillance of gastroenteritis at participating practices has improved its reporting on the aetiology of cases of GI infections [18].

Of recent, a new primary care database ResearchOne is now emerging as an alternative to CPRD, QResearch and THIN. TPP developed it in partnership with the University of Leeds and the UK Government Technology Strategy Board [19]. The data originates from patients' electronic care

records and clinical system, SystmOne, of which TPP is the proprietor. Launched in 2013, it comprises of 5000 providers including 2200 general practices, 1250 district nursing practices, 120 out of hours practices, 50 Child health units, 50 and minor injuries/A&E units [20]

Selection of dataset

Nearly all individuals in the UK are registered with a GP at the primary care level who oversees a patient's healthcare. Should a patient require further treatment or investigations at the secondary level (usually at a hospital), referrals are made by the GPs and the secondary care provided is generally fed back to the GPs as they act as the gatekeeper to the NHS. Hence, primary care records allow the follow up of individuals as it contains both exposure and outcome data. Further, it will enable the quantification of the primary outcomes of ReA and IBS, as these conditions are commonly diagnosed at the primary care level in the UK.

CPRD was chosen over other primary care databases due to its coverage and potential for linkage to other relevant datasets in the study of sequelae and associated risk factors. Further, CPRD is the most widely used of all three primary care databases for pharmacological based research and studies relying on the accuracy of coding for exposure and outcome measurement [14,15].

4.2.2 Hospital Episode Statistics

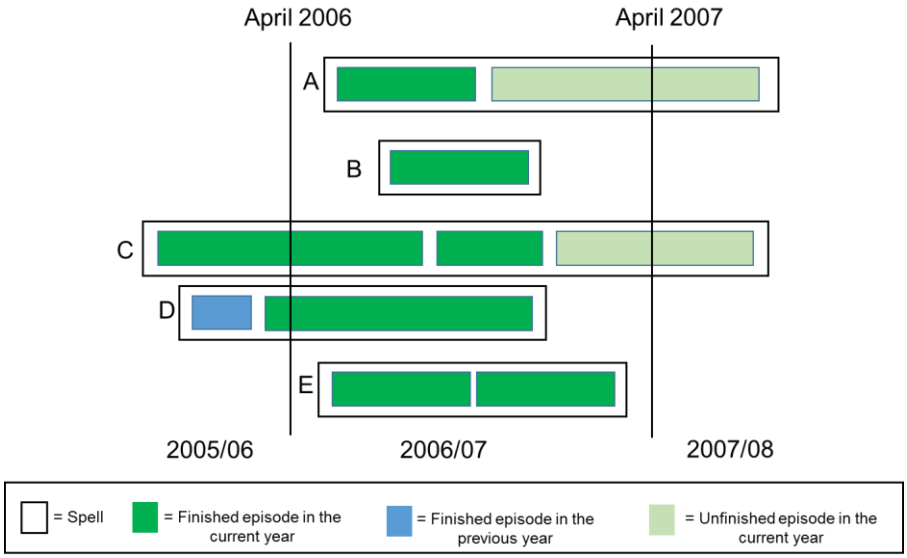
Overview of dataset

The Hospital Episode Statistics (HES), is a record-level administrative data warehouse managed by NHS Digital [21]. It was developed in the early 1980s to monitor hospital activity for management and planning of services with national coverage by the 1989/90 financial year. It is populated by taking extracts of routine data flows exchanged between health care providers and commissioners [21]. HES currently comprises three main data sets: Admitted patient care (APC), which includes inpatients and day cases; Outpatient visits and procedures, and Accident and Emergency (A&E) attendance. All datasets can be linked to CPRD; APC from 1997, Outpatients from 2003 while A&E from 2007 onwards.

HES APC contains information on patient demographics, clinical diagnoses and procedures performed while in hospital for every NHS hospital in England. Diagnoses in HES is coded using the WHO ICD-10 standard, while procedures are recorded using the Office of Population, Censuses and Surveys: Classification of Interventions and Procedures, 4th revision (OPCS-4) [22]. From 2004/05 onwards HES APC has been used for 'Payment by Results' (PbR), a pay-for-performance system for financial reimbursement of clinical activity within the NHS internal market.

Data files are structured according to the NHS fiscal year. Each row in HES APC indicates a 'Finished Consultant Episode' (FCE). FCE represents a continuous episode of care under one consultant. Each episode can contain more than 50 pieces of information, which includes patient demographics, hospital details, administrative details such as admission and discharge date and clinical details on diagnoses/treatment. Each episode is further organised into spells/hospitalisations (stay in hospital) which can be made up of one or more episodes [23]. Within each episode, a patient may have one or more diagnoses and procedures (Figure 4-1).

Figure 4-1 Relationship between episodes and spells in HES



Adapted from NHS Digital Spells Methodology [23].

Diagnoses are recorded in the primary diagnosis field and up to 20 additional diagnostic fields. These additional fields describe complications and co-morbid diagnoses. Where a definitive primary diagnosis is not possible, a code demonstrating the main symptom or abnormal findings may be used instead. For this thesis, any diagnosis recorded within the primary diagnosis and the additional 20 diagnostic fields will be used to determine the sequelae of interest. This will account for clinicians' varying recording practices if they record the main diagnosis in a secondary field. However, one limitation for this approach is that it may be difficult to differentiate whether the sequelae under study is a new episode of illness or an existing co-morbidity.

Approximately 75% of practices in England contributing data to CPRD have consented to the linkage of their data to HES [3]. Linked CPRD and HES provide further information on any diagnosis made both in primary and secondary care for a patient in temporal relation to an index diagnosis or prescription of interest.

Strengths and weaknesses of HES

A key strength of HES is the universal coverage of all NHS hospital activity in England. It has been used extensively for research and is ideally suited for precise estimation of outcomes for rare conditions, and identifying disease trends over time [24].

Diagnostic and procedure codes for exposure and outcome selection from HES data can be limited by the reporting clinician. Although clinicians undergo training on coding, discrepancies still exist amongst clinicians for coding preferences. However, the introduction of PbR has improved the coding of diagnoses and procedures. As with all databases not designed for research, there is a problem with missing data in HES, most especially the recording of ethnicity [12].

Selection of dataset

HES APC and Outpatients datasets were selected for linkage to CPRD. These will allow the capture of severe sequelae such as GBS and patients who do not go to their GP for their illness. Also, direct healthcare utilisation associated with selected GI infections and sequelae can be assessed in patients with a linked record in HES.

4.2.3 Public Health England Second Generation Surveillance System

The Second-Generation Surveillance System (SGSS) is a national database of notifications of positive laboratory reports of infection managed centrally by PHE, an Executive Agency of the DHSC. One of its remits is the surveillance of communicable diseases and threats to public health [25]. Consequently, it collates notification reports on several notifiable infections according to the Health Protection (Notification) Regulations 2010 [26]. SGSS was introduced in 2014 to replace LabBase2, a national database of positive reports of infections sent from local and regional laboratories, and additionally incorporates information on antimicrobial resistance previously stored in a separate database [27].

Electronic reports of positive results of *Campylobacter spp.* and NTS infections in England are available from 1983 onwards from both systems. They contain patient and laboratory demographics, phenotypic results of the isolated pathogen, type of laboratory tests, the origin of sample and, sometimes, travel information (both domestic and foreign) if recorded on the laboratory request form.

Selection of dataset

Availability of the patient's postcode, date of birth and NHS number can facilitate deterministic linkage to other datasets via the NHS Digital trusted third party linkage service [28]. This dataset was selected for linkage to HES APC and ONS mortality files to quantify outcomes not routinely diagnosed in primary care settings and deaths. Comparisons were made between this laboratory-linked data to CPRD-linked data to determine if there were differences in the sequelae captured.

4.2.4 Other datasets linked to CPRD and PHE SGSS

Office of National Statistics Mortality files

Annual deaths extracts are available from the Office of National Statistics mortality database. Mortality data are based on the information collected when deaths are certified and registered. It is a legal requirement to register all deaths since 1 July 1837 in England and Wales following The Births and Death Registrations Act (1836). Registration is completed by The Local Registration Service in partnership with the General Register Office [29].

Death registration usually occurs within five days of the date of death once the death is certified by a medical practitioner who issues the Medical Certificate of Cause of Death (MCCD) with the cause of death recorded [30]. In certain situations, such as a referral to the coroner when registration is delayed, the coroner sends information to the registrar, and this is used instead of the MCCD to register the death.

The death certificate used in England and Wales is compatible with that recommended by WHO. It is set out in two parts. Part I gives the condition or sequence of conditions leading directly to death and is used to derive the underlying cause of death, while Part II provides details of any associated conditions that contributed to the death but are not part of the causal sequence. WHO defines the underlying cause of death as "the disease or injury that initiated the train of events directly leading to death or the circumstances of the accident or violence that produced the fatal injury" [30].

Linkage to CPRD, SGSS, and HES is available for deaths registered from 1998 onwards. The underlying cause of death and other causes of death are coded according to the WHO ICD-10 standard. Deaths registered before 2001 use the WHO ICD-9 designation. This dataset was selected as it is the most comprehensive database on all registered deaths in the UK. Although deaths following the selected GI infections are rare, it will allow the estimation of deaths in the cohort via linking this dataset to patient's record in CPRD, and to patients with a laboratory-confirmed report in SGSS.

Indices of Multiple Deprivation

The index of multiple deprivation (IMD) is a relative measure of socio-economic status (SES) at a small area level across England [31]. Areas are ranked from least deprived to most deprived based on seven dimensions of deprivation (housing, employment, income, access to services, education and skills, crime, living environment). Each domain can itself be a composite score derived from two or more sub-domain indicators. An overall composite measure which is the index, is calculated as a weighted sum of the domain indices [31]. The overall ranking is of primary interest in this thesis rather than the actual score itself.

The first official Index of Deprivation in England were produced in 2000. Subsequent updates were produced in 2004, 2007, 2010, and 2015. The calculation is at the lower layer super output area (LSOA). Each LSOA has an average of 1,500 residents and around 400 households. The

measures are available at the patient level via linkage with patient postcode, and at the practice level for ecological studies using CPRD. Due to deductive disclosure of a patient's address, it was not possible to combine several years of deprivation data with linked CPRD records [32]. The IMD scores and rankings are in the public domain, and as such, it is possible to identify very small groups of LSOA via cross-tabulating two or more IMD versions [32].

IMD-2010 for England was selected for this thesis as it is the most recent update based on the 2001 census while data on indicators is from 2008. The IMD-2015 is based on the 2011 census with indicator data from 2012/13 [33]. Most of the patients in the cohort will enter the study before 2011. Hence IMD-2010 was deemed the best option.

Another indicator of deprivation in England is the Townsend score based on material deprivation using four census domains (household without a car, overcrowded households, households not owner-occupied, and persons unemployed) [34]. IMD was chosen over the Townsend score due to coverage of a larger number of domains that measure social and economic characteristics of neighbourhoods and not limited to material deprivation.

4.3 Ethical and legal considerations

All studies using CPRD are required to submit a protocol to the Independent Scientific Advisory Committee (ISAC) for assessment of the scientific rigour before a study can commence [35]. Applications to ISAC using CPRD data linked to established routine linkages such as HES and ONS do not require a separate ethics application. However, bespoke linkages, i.e. linkages not routinely performed, requires a separate ethics application and depending on the nature of the linkage may require further legal considerations.

To establish the bespoke linkage of PHE SGSS data to CPRD, the main ethical and legal considerations were:

1) Permission to share PHE data with an external organisation for purposes other than the surveillance of communicable disease. SGSS data is regulated under Regulation 3 of the NHS Act 2006 [36]. This allows PHE to collect and store information without the knowledge of individuals for communicable disease surveillance and other risks to public health. PHE self-regulates the use of its data. Hence, requests for linkage of SGSS to CPRD and other datasets were directed to the PHE Caldicott Guardians and the ISAC.

2) Linkage of data to CPRD uses patient identifiable information (PII) as defined by the Data Protection Act 1998. Bespoke linkages using data containing PII require support from section 251 under Regulation 5 of the NHS Act 2006 [36]. This enables a temporary lift of the common law duty of confidentiality to transfer PII to an applicant without the discloser being in breach of the common law of duty of confidentiality. Application for section 251 is made to the Confidential Advisory Group (CAG) of the Health Research Authority (HRA) [37]. In addition to CAG approval, ethics approval from an NHS research ethics committee was also required.

3) Ethics approval was also required if researchers have access to another data set which they can use to de-identify anonymised patients if they have access to pseudonymised data may include the same patients in the existing data held. As such, linkage of SGSS data to HES required ethics approval to ensure researchers would not attempt to de-identify anonymised patients if they have access to SGSS data via linkage to CPRD.

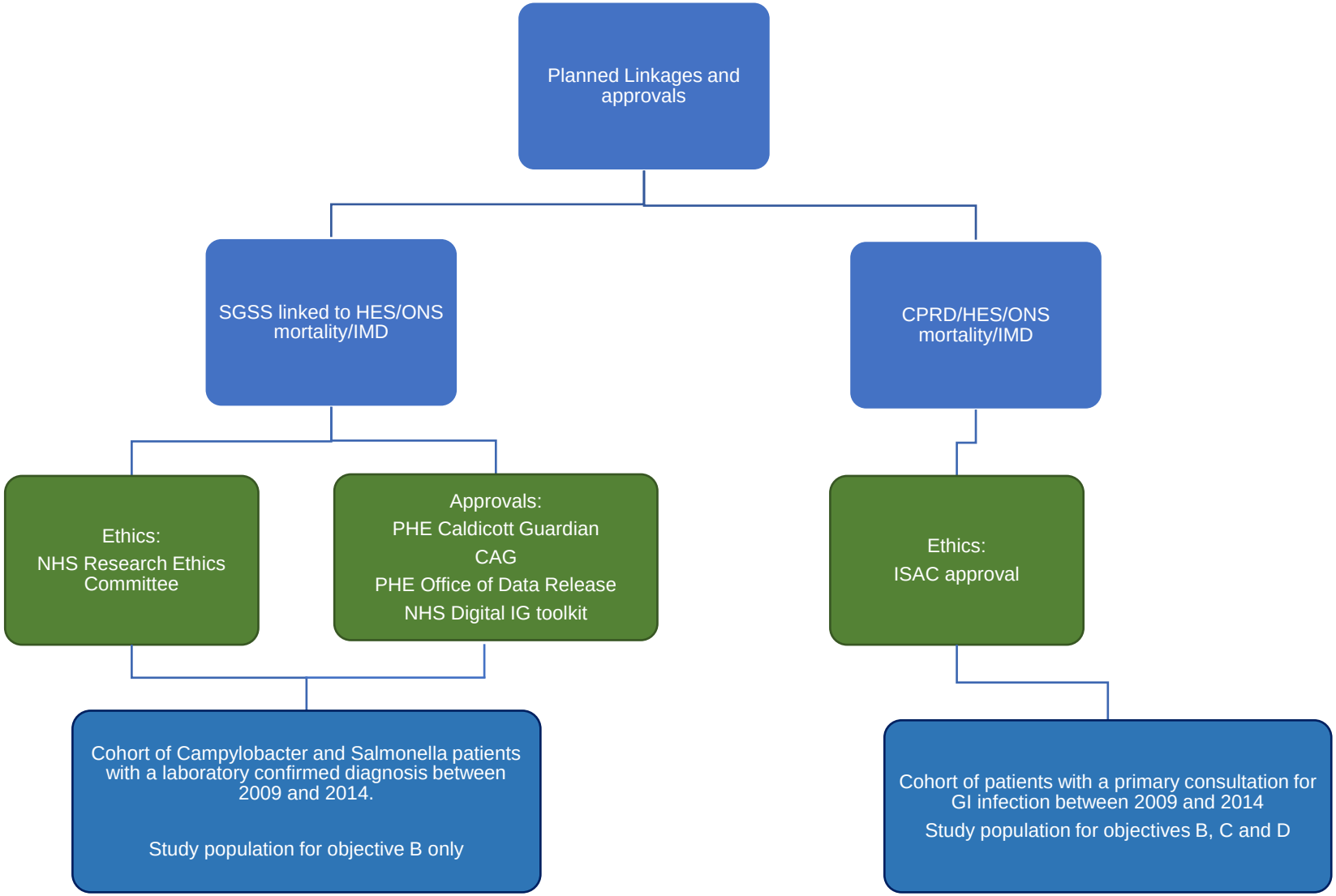
Before ethics approval could be granted it was crucial to have an information governance (IG) toolkit in place to ensure researchers have the infrastructure, adequate data storage and retrieval to deal with CPRD, SGSS, HES and ONS mortality files [38]. All required approvals were sought and granted for this research project except for the direct linkage of SGSS to CPRD (Appendix 4-1). The office of data release within PHE responsible for granting permission for PHE to share SGSS data for linkage to CPRD did not respond to the request for linkage for over two years since

the original request was made despite ethical approval from the NHS research ethics committee and the CAG.

4.4 Data linkage

Following delays in establishing a bespoke linkage of SGSS data to CPRD, only the routine linkages available with CPRD were used (Appendix 4-2). This required an amended protocol and a new ISAC approval (Appendix 4-3). Once this was granted, a deterministic linkage was performed using the NHS Digital trusted third-party service [28]. CPRD was linked to HES, ONS and IMD to allow the follow-up of individual patients who have records across all the linked data sources. In the absence of linkage of SGSS data to CPRD, SGSS data was also linked directly to HES APC and ONS mortality files to measure the incidence of sequelae and deaths amongst patients captured in national surveillance in comparison with those who present to general practice (Figure 4-3). This linkage was performed by personnel within PHE as they were granted access to HES APC and ONS mortality files by NHS Digital with permission for further linkage.

Figure 4-3 Relationship between linked data, ethics application and study population for research objectives



4.5 Study Design

This research project used a retrospective open cohort design to address objectives B, C and D, as stated in Chapter 2.5.4 (Figure 4-4). Data consisted of linked individual patients' primary care, laboratory, hospital, death, and deprivation records.

4.5.1 Inclusion Criteria

Objectives B and C (using CPRD with or without linkage to HES and ONS mortality)

Patients entered the study on the date of the first consultation for the diagnosis of *Campylobacter* or NTS from UTS CPRD practices with or without linkage to HES data and ONS mortality file between 1st January 2000 and 31st December 2015. Eligible patients were registered with the practice for a minimum of 12 months before study entry to ensure adequate recording of baseline covariates.

Objectives B only (using SGSS)

All laboratory patients with a confirmed diagnosis of *Campylobacter spp*. or NTS with a faecal/lower gastrointestinal tract (FLG) specimen between 1st January 2009 and 31st December 2014 with linkage to HES, with or without an ONS deaths record.

Objective D (using CPRD with linkage to HES)

All patients with relevant Read codes for the diagnosis of *Campylobacter* or NTS registered at UTS CPRD practices with linkage to HES data between 1st January 2000 and 31st December 2015. Eligible patients were registered with the practice for a minimum of 12 months before study entry to ensure adequate recording of baseline covariates.

4.5.2 Exclusion Criteria

Objectives B, C and D (using CPRD with or without linkage to HES)

Patients were excluded if:

- They did not have up to 12 months of registration at their GP practice before the date of the first consultation for the selected GI infection.

- They had multiple *Campylobacter* and NTS infection on the same date.

- They had a previous diagnosis of the conditions of interest (objectives B and C only), to ensure only incidence cases of sequelae were measured and not prevalent cases.

Objective B only (using SGSS)

Patients were excluded if they had multiple *Campylobacter* and NTS infection on the same specimen date. All non FLG and typhoidal *Salmonella* specimens were also excluded.

4.5.3 End of follow-up

Objectives 2, 3 and 4 CPRD with or without linkage to HES

For the descriptive and risk factor analysis (objectives B and C)

Follow-up ended at the earliest of date of death, date of sequelae, the patient's transfer out date and the practice's last collection date.

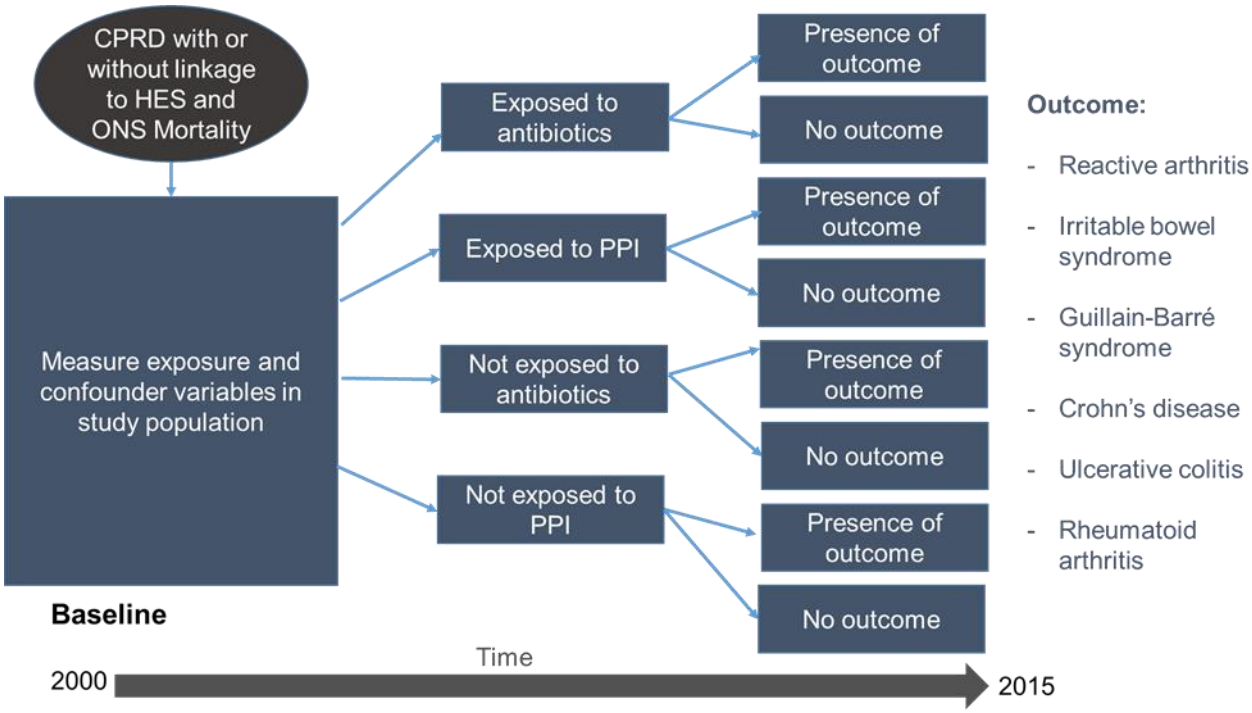
For the economic assessment (objective D)

End of follow-up was defined as the earliest of date of death, the patient's transfer out date and the practice's last collection date.

Objective B only (using SGSS)

End of follow-up was defined as the earliest of date of sequelae, date of death or last specimen date.

Figure 4-4 Retrospective cohort design of patients with *Campylobacter* or NTS infection, 2000 -2015



4.5.4 Study Population

Preliminary enquiry using CPRD Gold online access by the big data research group of the Nuffield Department of Primary Care Health Sciences, the University of Oxford in April 2016 indicated that a total of 26,524 patients with GI infection (23,527 patients with *Campylobacter* and 2,997 with NTS) were eligible for follow-up for the period, 1st January 2000 – 31st December 2015, based on the code list shown in Table 4-1. A total of 53,913, patients were provided by CPRD in the final data cut for the period 1st January 2000 – 31st December 2015 as they included patients with any mention of *Salmonella* or *Campylobacter* in the Read code.

Table 4-1 Read codes for the selection of patients

***Campylobacter* patients**	
A074300	*Campylobacter* gastrointestinal tract infection
A074311	Diarrhoea due to *Campylobacter jejuni*
A074312	*Campylobacter* enteritis
***NTS* patients**	
A020.12	Salmonella food poisoning
A020.00	Salmonella gastroenteritis
A020.11	Salmonellosis

Power calculation

CPRD data allows the assessment of the association of treatment with complications. The primary hypothesis is that antibiotic therapy of the acute infection is associated with increased risk of reactive arthritis. If 1% of those not treated with antibiotics develop reactive arthritis and 15% of cases are treated with antibiotics (conservative estimate based on preliminary data for antibiotic use), there is 99% power with 23,500 patients to detect a doubling of risk (to 2%). Where the risk is lower at 1.5%, the study will have approximately 70% power with 23,500 cases to detect a RR of 1.5. If the risk in those with antibiotics is higher at 3%, the study will have approximately 99% power with 23,500 patients to detect a risk of 4.5% (RR 1.5). Power decreases if a lower proportion of the cohort receives antibiotics and increases if a higher proportion receives antibiotics.

4.6 Data management

4.6.1 Data acquisition

CPRD linked to HES/ONS mortality/IMD-2010

Raw data were received from the CPRD in the generic American Standard Code for Information Interchange (ASCII) format, via download from an encrypted file exchange online server. The raw data extracts acquired for this thesis required further exploration to address the specified research questions. CPRD records for each patient in the cohort were supplied according to the 10-part structure of CPRD. HES, ONS, and IMD files were supplied as individual files with HES files having further subcategories (Appendix 4-4). Each file contained the patient's unique identifier assigned by CPRD. This id was used to link an individual patient's record together. It was possible for a patient to have several multiple observations on the same date.

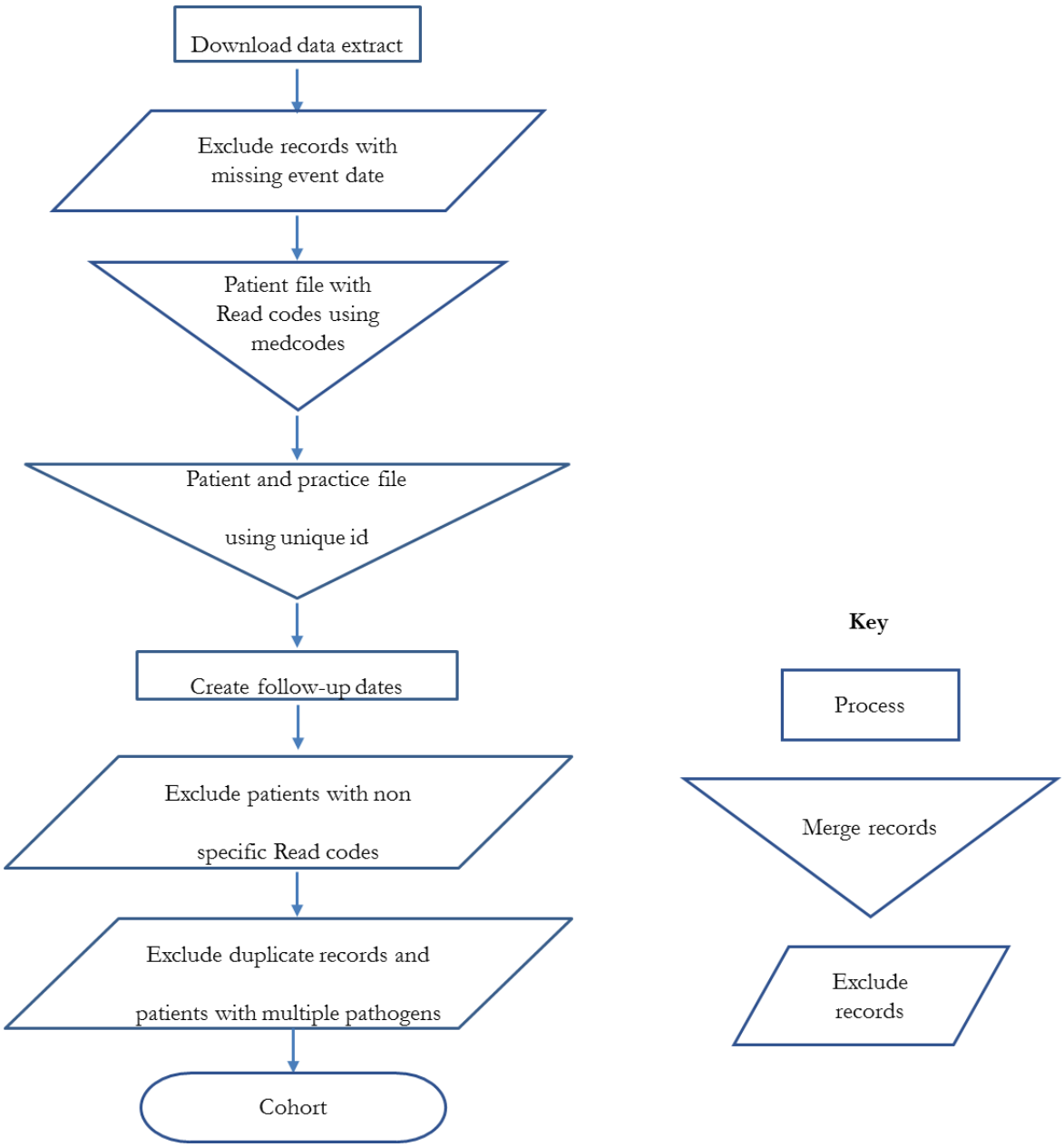
PHE SGSS linked to HES/ONS mortality/IMD-2010

Raw data were received from the PHE in Microsoft Excel, via download from an encrypted file exchange online server. The raw data extracts acquired for this thesis required cleaning and deriving variables to address the specified research questions. SGSS files were supplied with linked IMD quintiles. HES and ONS were supplied as individual files. Each file contained the patient's unique identifier assigned by PHE. This id was used to link an individual patient's record together. It was possible for a patient to have multiple tests on the same date.

4.6.2 Data cleaning

STATA 14.0 was used for data cleaning and management. See Figure 4-5 for key steps in creating the final cohort for analysis.

Figure 4-5 Essential cleaning steps for the final cohort



4.7 Definitions used within this thesis

The datasets used for this thesis were not collected for research purposes. Some of the variables used for analyses were derived from the dataset, and several key definitions were adopted for this thesis.

To follow-up patients with *Campylobacter* or NTS infections in assessing sequelae development; it is crucial to determine what constitutes a case of *Campylobacter* or NTS GI infection and identify the onset date of illness. However, the onset of these GI infections is usually unattainable without an enhanced surveillance system following up patients with questionnaires on historical events leading up to the illness or through recruitment and follow-up of patients in a study.

Patients with any mention of *Campylobacter* or NTS infection in the consultation file who were eligible for entry were provided by CPRD. Further exploration to determine if they were variation in the Read codes listed in Table 4-1 across different regions and practices for the patients provided by CPRD indicated a preference for *Campylobacter* GI tract infection (A074300) and *Salmonella* gastroenteritis (A020.00) Read codes (Appendix 4-5). These Read codes have also been used by other researchers in determining the incidence of these GI infections within primary care [39]. These Read codes are sensitive and do not include codes for "gastroenteritis" which is commonly recorded upon clinical examination and does not indicate the aetiology of infection [10]. Hence, before a GP can use the Read codes selected for the study population, confirmation of the infecting pathogen through laboratory tests should have been performed. **As such a case was defined as having the first consultation for *Campylobacter* or NTS gastroenteritis based on the following Read codes – A074300, A074311, A074312, A020.12 and A020.00 (Table 4-1) as recorded in the consultation file.**

However, within CPRD, it was possible to have a Read code for *Campylobacter* or NTS infection without a corresponding laboratory test. Further, where appropriate laboratory tests were

recorded, such as stool culture, results were only available for two per cent of these patients (Table 4-2). This may be a function of GP behaviour in the use of Read codes to record laboratory test results. Some studies have demonstrated inconsistencies in the request and recording of stool culture following suspected GI infections, while others suggest laboratory results are missing not at random because tests results with a numerical value are more likely to be recorded systematically than results which indicate presence/absence of disease which may only be available within the free text section [40]. This free text section is not readily available to researchers.

Therefore, the date when a Read code for *Campylobacter* or NTS gastroenteritis was recorded was set as the **Index date** as a marker for date of onset of illness as the date of laboratory test could not be adopted**.** The **Index date** for each patient was used to determine any temporal association with both exposures and outcomes of interest in the follow-up from the onset of their GI infection to development of sequelae (Figure 4-6). For patients selected from SGSS, the specimen date was used as the index date.

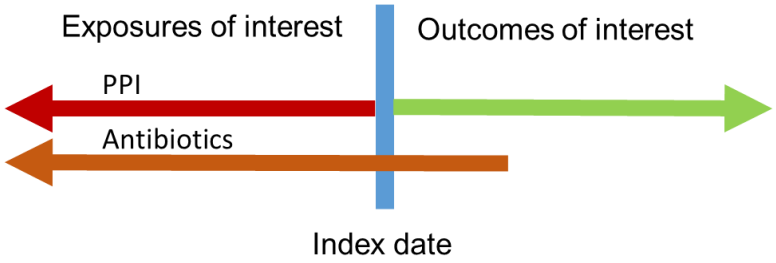
Table 4-2. Laboratory testing and results for all CPRD patients who were selected using an expansive code list by the MHRA

Read code for entry	All patients	Laboratory tests†	Results	Positive results
Campylobacter	24,186	8,675	1,199	337
NTS	9,381	6,260	347	109
Negative for *Campylobacter*/NTS	10,383	9,698	8	1
Serology for *Campylobacter*/NTS	9,963	5,707	42	1
Total	53,913	30,340	1,596	448

†The cohort of patients provided by CPRD was merged with the corresponding test file to determine if patients had a code recorded for stool culture (entity type 235) or examination of faeces (entity type 316). Tests were selected if the test date recorded was within a month (30 days before or 30 days after) of the index date for entry into the cohort to allow for a delay in recording.

GI infections are common. It was possible for a patient to have multiple episodes of gastroenteritis. **Repeat episodes** refer to recorded recurrent episodes of gastroenteritis by the same pathogen within a month of the preceding episode in CPRD (to allow for a delay in reporting of laboratory test results) and within 14 days in SGSS. Repeat episodes were treated as the same episode of illness. Hence only the earliest date was selected as the Index date for the episode.

Figure 4-6 Relationship between Index date, Exposures and Outcomes of interest



4.7.1 Exposure variables

Exposures were determined from prescription records within the CPRD therapy data files for three classes of antibiotics (quinolones, macrolides, and cephalosporins) and PPI (Appendix 4-6). The exposure window and patient criteria are listed in Table 4-2. Data exploration was required to finalise the exposure window for antibiotics. The daily prescription rate of antibiotics in the 30 days before, 30 days after the index date and including the index date for patients in the cohort were assessed. The 7-days before and after index data was selected as the exposure window to take account of those who may have been prescribed antibiotics in the days before confirmation of infection and for those who were prescribed antibiotics for their GI infection after diagnosis on the index date. Figure 4-7 shows the causal relationship between antibiotics and sequelae onset.

Figure 4-7 Causal diagram showing the effect of antibiotic usage and development of sequelae

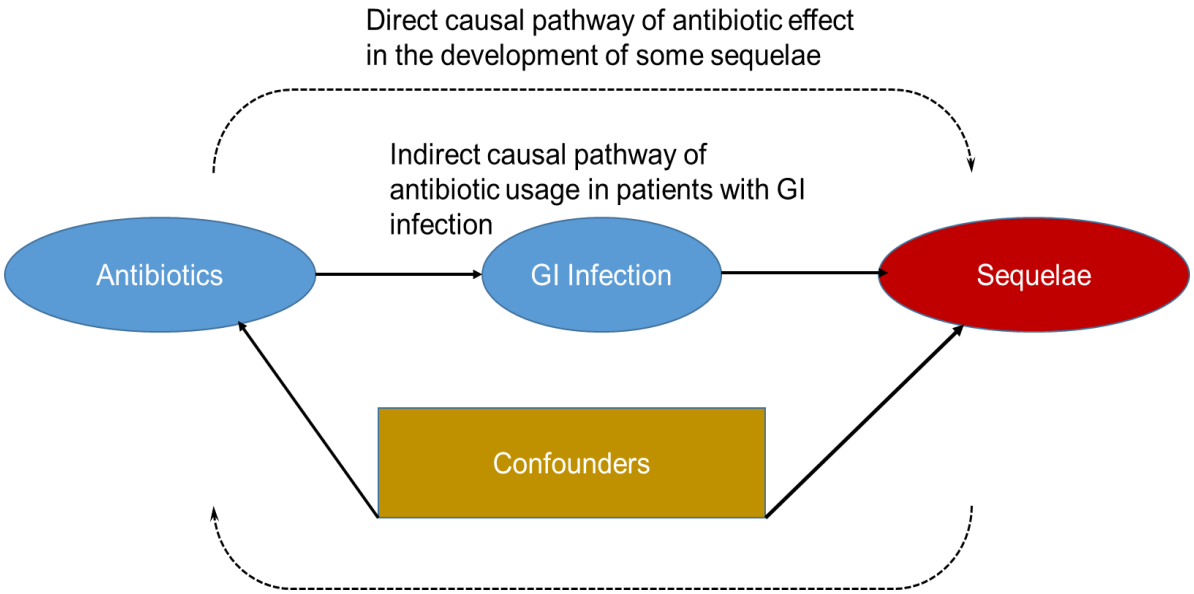


Table 4-2 Patient selection criteria for exposure of interests

Exposure variable	Definition in CPRD
Antibiotics – quinolones	Product codes for the first prescription of any quinolone class of antibiotics up to 7 days before "Index date" and up to 7 days after (Appendix 4-6).
Antibiotics – macrolides	Product codes for the first prescription of any macrolide class of antibiotics up to 7 days before "Index date" and up to 7 days after (Appendix 4-6).
Antibiotics – cephalosporins	Product codes for the first prescription of any cephalosporins class of antibiotics up to 7 days before "Index date" and up to 7 days after (Appendix 4-6).
Proton pump inhibitors	Product codes for the first prescription of any PPI up to 12 months before "Index date" for patients aged 18 years and over (Appendix 4-6).

4.7.2 Outcomes – Chapters 5 and 6

The primary outcomes of interest were the development of ReA and IBS following *Campylobacter* or NTS infection as they were the frequently reported in the systematic review (Chapter 3) conducted and they are commonly diagnosed within primary care settings [41]. Secondary outcomes include the development of GBS, IBD, UC, CD and Rheumatoid arthritis (Read codes in

Appendix 4-7, and ICD-9 & ICD-10 codes in Appendix 4-8). The selection criteria for the outcomes are listed in Table 4-3.

Table 4-3 Selection criteria for the outcomes of interest

Outcome variable	**Definition in CPRD**	**Definition in HES**
Reactive arthritis (ReA)	Any occurrence of Read codes for reactive arthritis up to 12 months after "Index date".	ICD-10 code for reactive arthritis using "any mentions" in the diagnostic category.
Guillain-Barré Syndrome (GBS)	Any occurrence of Read codes for Guillain-Barré syndrome up to 12 months. after "Index date".	ICD-10 code for GBS using "any mentions" in the diagnostic category.
Irritable bowel syndrome (IBS)	Any occurrence of Read codes for Irritable bowel syndrome up to 12 months after "Index date".	ICD-10 code for IBS using "any mentions" in the diagnostic category.
Ulcerative colitis (UC)	Any occurrence of Read codes for ulcerative colitis up to 12 months after "Index date".	ICD-10 code for ulcerative colitis using "any mentions" in the diagnostic category and OPCS-4 code for radiology and histology.
Crohn's disease (CD)	Read codes for the first consultation of Crohn's disease up to 12 months after "Index date".	ICD-10 code for Crohn's disease using "any mentions" and OPCS-4 code for radiology and histology.

Outcome variable	Definition in CPRD	Definition in HES
Rheumatoid arthritis (RA)	Read codes for the first consultation of rheumatoid arthritis up to 12 months after "Index date".	ICD-10 code for rheumatoid arthritis using "any mentions" in the diagnostic category.

4.7.3 Outcomes – Chapter 7

Direct healthcare resource use was assessed for patients with linked CPRD and HES data only. Primary care resource use for each patient was extracted from CPRD. It included primary care consultations, tests, and prescriptions. Secondary care resource use for each patient was extracted from HES. These include inpatient admissions, outpatient visits, and procedures. Standard procedures to prepare HES data for costings was followed. Unit costs for each healthcare resource domain were obtained from relevant published cost estimates. Selection criteria for each healthcare resource and data sources for costings are described in detail in Chapter 7.

4.7.4 Covariates

The explanatory variables listed below may be risk factors for the above outcomes and associated with the exposures of interest. They were adjusted for in statistical analysis in Chapter 6 but are not of primary interest themselves.

Age at sequelae [Continuous; Years]

Patients' exact date of birth was not available, only birth year to preserve anonymity. The date of birth was estimated through taking the midpoint in the year represented by the "birth year" variable within the patient file of CPRD (i.e. June 1st) and subtracting the date from the individual's consultation date.

Age at complication [Categorical; Years]

Patients age at sequelae were categorised into four age bands (0-17, 18-44, 46-64 and 65 and above) to tests any association between antibiotics/PPI and sequelae onset (objective C, Chapter 6). The same categorisation was also used for patients' stratification of healthcare resource use and costs (objective D, Chapter 7).

Sex– [Binary; No units]

Sex was obtained from the patient file of CPRD, where the "sex" variable indexes it as 1 for male and 2 for female. It was coded as 0 for male and 1 for female.

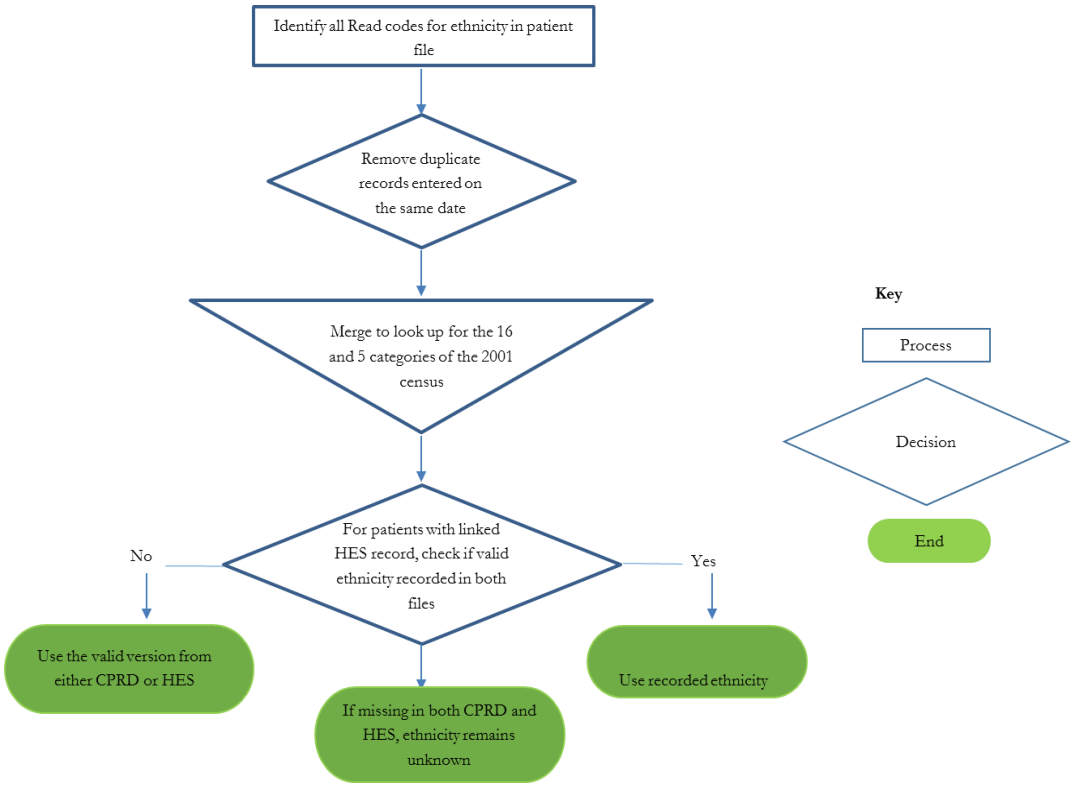
Ethnicity - [Categorical; No units]

Ethnicity information was obtained from the additional clinical files in CPRD using Read codes according to the 1991 census (9i), 2001 census (9S), 2011 census (9t) and other classifications of ethnicity and country of origin (9T). The obtained ethnicity codes were mapped to the 16 classification levels of the 2001 census and the five-classification category of the 1991 census for patients with ethnicity recorded before the 2001 census. Where ethnicity was not recorded in the CPRD, if the patient had a linked record in HES, the ethnicity information was used if available. HES also uses the 16-classification levels for ethnicity according to the 2001 census (Table 4-4). However, for records before 2001, the 1991 census classification is used. If a patient had inconsistent ethnicity recording using the 16-classification level that could not be mapped to the same category using the five-classification level, then ethnicity was recorded as missing (Figure 4-8).

Table 4-4 Ethnicity classification

16 groups – 2001 Census	5 Categories – Higher level
1 British	**1 White**
2 Irish	
3 Any other White background	
4 White and Black Caribbean	**2 Mixed**
5 White and Black African	
6 White and Asian	
7 Any other mixed background	
8 Indian	**3 Asian or Asian British**
9 Pakistani	
10 Bangladeshi	
11 Any other Asian background	
12 Caribbean	**4 Black or Black British**
13 African	
14 Any other Black background	
15 Chinese	**5 Chinese or Other Group**
16 Any other ethnic group	

Figure 4-8 Algorithm for determining ethnicity in both CPRD and HES



Deprivation- [Categorical; No units]

Individual-level deprivation data were available for patients with linkage to IMD 2010 (England only). The overall ranking score in the IMD 2010 recorded at the LSOA for each patient in quintiles.

Smoking status – [Categorical; No units]

Smoking was obtained from the clinical file and the additional file, where it is indexed as 0-No data, 1 for –Yes, 2-No and 3-Ex-smoker.

Charlson comorbidity index – [Score; No units]

The Charlson Comorbidity Index, CCI, classifies a patient according to their disease burden by accounting for both the number and severity of the comorbidities. The CCI and associated Read codes for selection are listed in Appendix 4-9.

4.8 Statistical Analyses

All statistical analyses were performed in STATA version 14 (Stata Corporation, College Station, Texas, USA). Statistical significance was accepted for $P < 0.05$ using two-tailed tests unless otherwise stated. Corresponding 95% confidence intervals were reported.

4.8.1 Statistical analysis for chapter five

Primary analyses

The incidence of sequelae was estimated among patients with *Campylobacter* and NTS infections selected from the CPRD-linked and SGSS-linked datasets within 1-, 3-, 6-, and 12-months post-infection, respectively. It was reported as incidence rate per 1,000 person years (py) of follow up with the corresponding 95% confidence interval. Differences in the distribution of exposures,

covariates and outcomes were examined using *t*-tests of statistical significance for continuous variables and chi-squared tests for categorical variables.

Sensitivity analyses

Baseline levels of monthly sequelae rate in patients from both CPRD-linked and SGSS-linked data were calculated up to five years before the index date and up to one year after the index date. Where there was a high level of background noise, the lowess function in STATA was applied [42]. It performs a locally weighted regression of the crude rate of sequelae on month as a running line for smoothness of good fit to visualise any trend in the monthly rate of sequelae[43,44]. This was preferred over running means which can be prone to bias at the extremes of ranges because the lowess gives more weight to the closest observations [42].

4.8.2 Statistical analysis for chapter six

Primary analyses

A logistic regression model was adopted to assess the effect of treatments on the risk of sequelae onset following confirmed infection with *Campylobacter* or NTS at the class level for antibiotics (macrolides, quinolones and cephalosporins), and all PPI reported.

The analysis included the calculation of odds ratios with confidence intervals. Counts with small numbers i.e. less than five were not reported, thereby eliminating the possibility of unintentional deductive disclosure. Multivariate analysis was used to assess any interaction between, age, sex, smoking status, CCI index and sequelae.

To reduce the risk of a Type I error occurring due to multiple statistical testing for multiple outcomes and exposures; the following approaches were adopted:

- For the primary outcomes of the study (ReA and IBS), no correction was made for multiple outcomes and exposures. The significance level was set at $P < 0.05$.

- For the secondary outcomes, adjustments for multiple outcomes and exposures were made to reduce the likelihood of a Type I error by:

- Using a lower significance level of $P<0.01$ to make allowance for the multiplicity of *P*-values.

- For events with small numbers, to preclude fitting of the statistical model (e.g. for deaths), no further statistical tests.

Sensitivity analysis

Patients without an IMD-quintile were excluded, and the multivariate logistic regression model was refitted to assess any interaction between, age, sex, smoking status, CCI index, IMD and sequelae.

Secondary analyses

Further model adjustments were made by:

- Assessing any temporal association between sequelae onset and use of antibiotics or PPI by using the onset of sequelae within 1-, 3-, 6-, and 12-months as the independent variable, while prescription for antibiotics or PPI was the dependent variable.
- The dose-response relationship between PPI and sequelae was considered using the total number of prescriptions within 12-months before the selected GI infection. PPI as an independent variable was treated as a categorical variable (0 – no PPI prescription, 1 – up to 5 PPI received, 2 - between 6 -10 PPI received and 3 > 10 PPI received). This was used to fit a logistic regression model adjusted for covariates, which were significantly associated with sequelae onset. STATA's margins function was used to compute the predictive margins for the differences in levels of margins if the covariate values are changed in the fitted model.

Tests for linear trend

For ordinal covariates such as age group, IMD-quintile and the total number of PPI, linearity was assessed by visually inspecting the predicted margins from fitting the model using STATA's margins command. This was followed by comparing each level of the categorical level against the reference and also against the next level to determine if linearity existed across all the levels using STATA's contrast command [45–47]. The differences in the comparisons were reported alongside their 95% confidence intervals. Significance was determined at $P < 0.05$.

4.8.3 Statistical analysis for chapter seven

This is described in detail in Chapter 7. Briefly, the impact of the diagnosis of *Campylobacter* and NTS infections and subsequent sequelae on the average resource use and costs incurred by each patient within primary and secondary care settings was assessed. The period before and following a diagnosis of *Campylobacter* or NTS for patients in CPRD with a linked record in HES was considered. Analyses were stratified by resource use and cost category of interest, as well as by relevant socio-demographic characteristics of patients. Average quarterly and annual amounts of healthcare resource use and associated costs were calculated and further stratified by patients with the selected GI infections only and those that developed the sequelae of interest.

Consultations, referrals, tests, hospital admissions and outpatients' visits/procedures were treated as continuous variables and reported as the number of events per patient per quarter/year. Resource use rates and mean costs before and after diagnosis were reported together with their standard errors. Rates and mean differences in observed resource use and costs between the two periods were reported alongside 95% confidence intervals. Statistical differences in mean estimates were evaluated using Student's two-sided t-test.

4.9 Chapter summary

This chapter described the overall methodology used in the thesis, including data sources and study design for three of the research objectives in this thesis.

The adaptation of the chosen data sources to address the research objectives, the rationale for key definitions, algorithms for exposure, covariates and outcomes were also described.

4.10 References

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Chapter 5

Incidence of sequelae following selected gastrointestinal infections

5.1 Overview

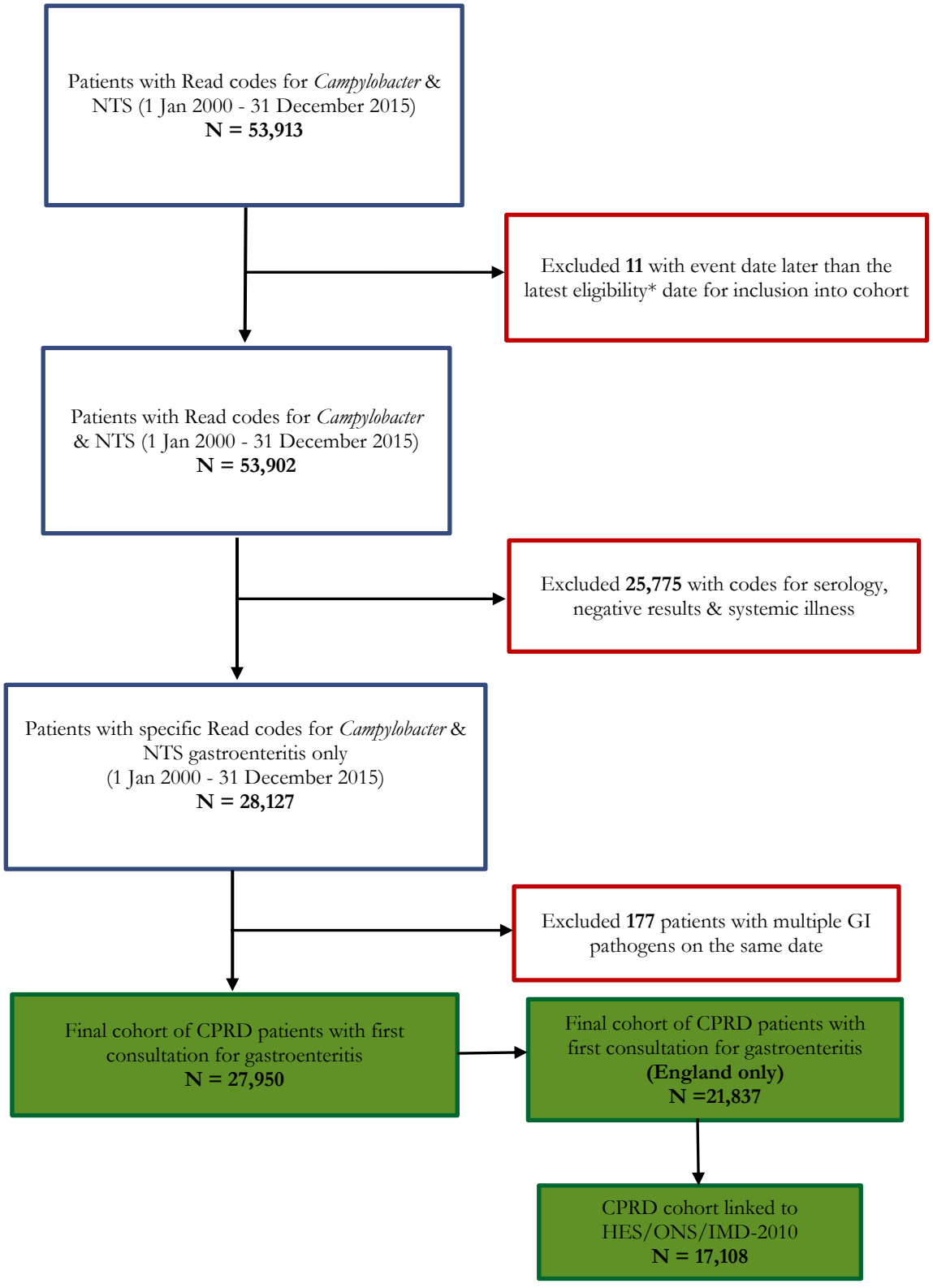
This chapter describes the characteristics of patients with selected GI infections from SGSS and CPRD with the linked hospital, deprivation and deaths records who were followed up until sequelae onset. Incidence of sequelae from CPRD linked records and SGSS linked records were compared to determine any differences in the data sources in the rate of recorded sequelae. Methods and statistical analyses were outlined in Chapter 4. The patterns of incidence observed are presented and discussed with further implications of the main findings, overall strength and limitations in Chapter 8.

***Objective B**: To identify the distribution of sequelae across different ages, gender and region following infection with Campylobacter and NTS in England using laboratory, primary and secondary care data.*

5.2 Study Population

A total of 27,590 CPRD patients met the case definition for NTS (n = 3,584) and *Campylobacter* (n = 24,006) GI infections recorded within the study period, 1 January 2000 - 31 December 2015 (Figure 1). Approximately 80% of patients (21,837/27,950) were from England.

Figure 5-1 Flow chart of selection of CPRD patients



*Latest eligible date for entry into cohort is based on the earliest of transfer out date from a practice, date of death or date of practice last contribution.

Between 1 January 2009 and 31 December 2014, 359,474 laboratory confirmed reports of selected GI infections (NTS, n =43,511, and *Campylobacter*, n = 315,963) with an FLG specimen were reported to SGSS for England only.

This represents an overall 1.6-fold difference in the number of patients with the selected GI infections captured by both SGSS and CPRD datasets for NTS and *Campylobacter* infections in England when CPRD coverage is considered (Table 5-1 and Figure 5-2).

Table 5-1 CPRD and SGSS patients with selected GI infections in England, 2009-2014

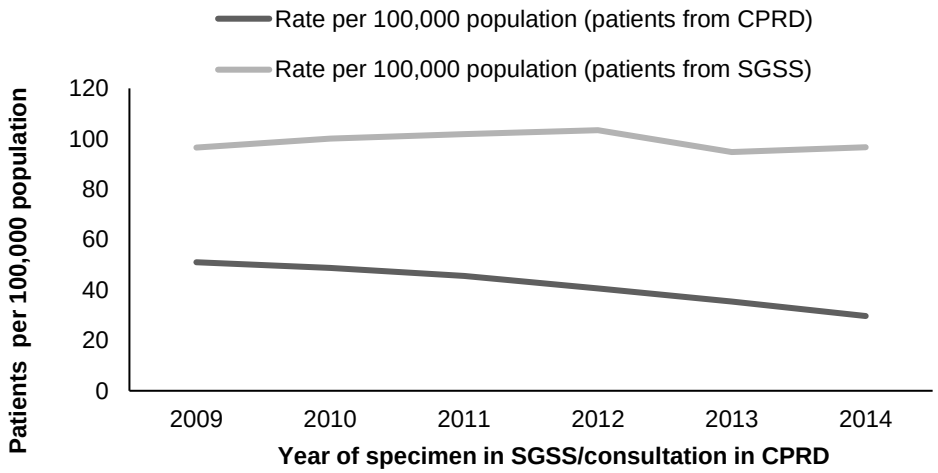
	Campylobacter						
	2009	2010	2011	2012	2013	2014	Total
SGSS counts	50,387	52,712	54,058	55,315	51,032	52,459	315,963
CPRD counts	1,396	1,346	1,268	1,138	1,000	845	6,993
CPRD population multiplier[1]	26,621	25,667	24,180	21,701	19,069	16,114	133,352
Rate per 100,000 population (patients from CPRD)[2]	48.5	46.3	43.3	38.5	33.6	28.2	238.5
Rate per 100,000 population (patients from SGSS)[2]	96.5	100.1	101.8	103.4	94.7	96.6	595.0
	NTS						
	2009	2010	2011	2012	2013	2014	Total
SGSS counts	8,479	7,631	7,582	7,027	6,532	6,260	43,511
CPRD counts	174	156	96	109	86	77	698
CPRD population multiplier[1]	3,318	2,975	1,831	2,079	1,640	1,468	13,310
Rate per 100,000 population (patients from CPRD)[2]	6.0	5.4	3.3	3.7	2.9	2.6	23.8
Rate per 100,000 population (patients from SGSS)[2]	16.2	14.5	14.3	13.1	12.1	11.5	81.9

Table 5-1 shows the differences in what is captured on GI infections from both data sources. The data cut from CPRD for this thesis has a coverage of 6.9% of the UK population, of which, 80% are from England. Taking this into account, the number of patients with GI infections from CPRD can be multiplied by the coverage factor of 0.0552 to determine the overall rate of GI infections that would have been captured by CPRD if data covers the entire England population. [1]The number of patients with GI infections are multiplied by a factor of 0.0524 to estimate the overall number of GI infections in England. [2]ONS mid-population estimates for England for each year of interest is the denominator. For the total column, ONS mid-population estimate for 2011 is the denominator.

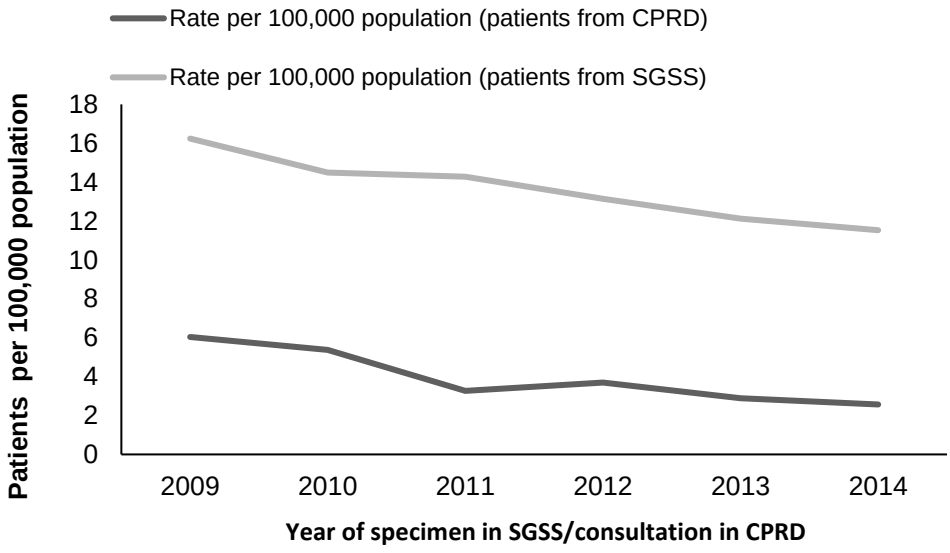
Overall, there was an opposite trend in the number of *Campylobacter* patients selected from CPRD in comparison to SGSS, while a similar trend was observed for NTS patients selected from both datasets between 2009 and 2014 (Figure 5-2).

Figure 5-2 Comparison of patients with a confirmed laboratory report for *Campylobacter* or NTS infections from SGSS and patients with a consultation for NTS infections or CPRD, England only, 2009-2014

***Campylobacter* patients**



NTS patients



5.3 Baseline characteristics

Table 5-2 summarises the baseline characteristics of patients with the selected GI infections from both data sources. Age and sex information was complete for CPRD patients but missing for less than one per cent of SGSS patients. Across both CPRD and SGSS data, *Campylobacter* patients were older and were more likely to be males in comparison to NTS patients. Children less than five years old were disproportionately affected in comparison with the rest of the population of NTS patients from both data sources (Table 5-2).

It was not possible to make a direct comparison of SGSS patients with CPRD at the regional level due to boundary differences for South East, South East Coast and South Central. Where the boundaries were comparable, the proportion of *Campylobacter* and NTS were similar across the regions in both data sources except for SGSS, which had a higher proportion of *Campylobacter* patients from the Yorkshire and The Humber, and a higher proportion of NTS patients from London in comparison with CPRD (Table 5.2).

Linkage to HES and ONS was available for the majority of CPRD patients from England (78%, 17,108/21,837) but less than a quarter of SGSS patients were linked to HES (23.6%, 84,692/359,474). There were no differences in the age and sex profile of patients with a linked record in comparison to those without amongst CPRD patients (Appendix 5-1). For SGSS, patients with linked records were older (NTS, mean age 33.4 vs 30.8 years; *Campylobacter* mean age 46.1 vs 38.9 years) and more likely to be females in comparison with those without a linked record (Appendix 5-1). Patient-level deprivation for England was complete for all SGSS patients but unavailable for approximately 20% of CPRD patients who did not have linked records. There was a downward trend across the IMD quintiles for SGSS *Campylobacter* patients (least deprived, 14.8% vs most deprived 23.2%), while the opposite pattern was observed amongst CPRD *Campylobacter* patients (least deprived, 18.3% vs most deprived

11.3%, *P* <0.001). NTS patients had a similar pattern of SES across the IMD quintiles for both data sources (Table 5-2).

There were considerable missing data for ethnicity (50% in CPRD and 96% in SGSS). Of the patients with recorded ethnicity, "White" was frequently recorded, while the least recorded was "Mixed" ethnic group (Table 5.2).

Additional information on travel and origin of the specimen were available from SGSS. Travel information was available for only 20% of *Campylobacter* patients and about half of NTS patients. About a third of NTS patients laboratory reports indicated foreign travel, with less than one per cent of *Campylobacter* reports. Where the organisation requesting a specimen for testing was available (70% for *Campylobacter* vs 5% for NTS), the majority of patients with *Campylobacter* had specimens originating from GP Practices (Table 5-2).

The CCI was used as an indication of existing comorbid conditions amongst CPRD patients. Over half of the cohort (66.0%, 14,419/21,837) did not have a record for any of the 17 disease domains making up the index. Of those with a comorbid condition, "1" was frequently recorded indicating the presence of only one comorbid condition. Considering the 17 individual disease domains included in the CCI, chronic pulmonary disease was the most recorded in the cohort (18.9%, 4,121/21,837).

Smoking information was missing for six per cent of the cohort. Where smoking status was recorded, patients were more likely to be non-smokers (63.6%, 13,887/21,837) (Table 5-2).

Table 5-2 Baseline characteristics of patients with a consultation for gastroenteritis in CPRD, 1 January 2000 - 31 December 2015 (England only), in comparison with patients with a confirmed laboratory report for gastroenteritis from SGSS, 1 January 2009 - 31 December 2009

	CPRD, 2000-2015			SGSS, 2009 -2014		
	Campylobacter **N = 18,964**	***NTS*** **N = 2,873**		***Campylobacter*** **N = 315,963**	***NTS*** **N = 43,511**	
	N (%)	**N (%)**	***P*-value**	**N (%)**	**N (%)**	***P*-value**
Age at entry (years)						
Mean (Sd)	44.8 (20.9)	37.0 (22.9)	<0.001	44.6 (22.8)	32.5 (24.4)	<0.001
Age group (years)						
0-4	911 (4.8)	289 (10.1)	<0.001	19,700 (6.2)	8,471 (19.5)	<0.001
5-14	828 (4.4)	366 (12.7)		16,278 (5.2)	4,640 (10.7)	
15-24	1,673 (8.8)	285 (9.9)		33,687 (10.7)	5,230 (12.0)	
25-44	5,518 (29.1)	764 (26.6)		78,324 (24.8)	4,690 (10.8)	
45-64	6,417 (33.8)	802 (27.9)		97,492 (30.9)	9,709 (22.3)	
65+	3,617 (19.1)	367 (12.8)		8,363 (2.7)	5,328 (12.2)	
Sex						
Male	9,908 (52.2)	1,376 (47.9)	<0.001	167,424 (53.0)	21,396 (49.2)	<0.001
Female	9,056 (47.8)	1,497 (52.1)		147,172 (46.6)	21,364 (49.1)	
Unknown	-	-		1,367 (0.4)	751 (1.7)	
Region						
North East	442 (2.3)	71 (2.5)	<0.001	18,586 (5.9)	2,150 (4.9)	<0.001
North West	2,705 (14.3)	365 (12.7)		38,579 (12.2)	5,313 (12.2)	
Yorkshire & The Humber	745 (3.9)	120 (4.2)		34,510 (10.9)	4,583 (10.5)	
East Midlands	800 (4.2)	150 (5.2)		25,044 (7.9)	3,136 (7.2)	
West Midlands	2,103 (11.1)	262 (9.1)		34,370 (10.9)	3,763 (8.6)	
East of England	2,290 (12.1)	361 (5.2)		37,052 (11.7)	4,801 (11)	
London	1,650 (8.7)	402 (14.0)		28,324 (9)	7,776 (17.9)	
South West	2,406 (12.7)	318 (11.1)		44,569 (14.1)	4,364 (10)	
South East Coast	2,457 (13.0)	325 (11.3)		54,929 (17.4)	7,625 (17.5)	
South Central	3,366 (17.7)	499 (17.4)		-	-	
Index of Multiple Deprivation (IMD)						

	CPRD, 2000-2015			SGSS, 2009 -2014		
	Campylobacter **N = 18,964**	***NTS*** **N = 2,873**		***Campylobacter*** **N = 315,963**	***NTS*** **N = 43,511**	
	N (%)	**N (%)**	***P*-value**	**N (%)**	**N (%)**	***P*-value**
1-Least deprived	4,441 (23.4)	624 (21.7)	<0.001	46,909 (14.8)	8,689 (20)	<0.001
2	3,892 (20.5)	528 (18.4)		57,349 (18.2)	9,213 (21.2)	
3	2,931 (15.5)	455 (15.8)		66,057 (20.9)	8,680 (19.9)	
4	2,247 (11.8)	380 (13.2)		72,404 (22.9)	9,391 (21.6)	
5-Most deprived	1,349 (7.1)	253 (8.8)		73,244 (23.2)	7,538 (17.3)	
Missing	4,104 (21.6)	633 (22.0)		-	-	
Ethnicity						
Asian or Asian British	228 (1.2)	79 (2.7)	<0.001	12,676 (4)	83 (0.2)	-
Black or Black British	68 (0.4)	47 (1.6)		881 (0.3)	17 (<0.01)	
Chinese or other	88 (0.5)	27 (0.9)		397 (0.1)	8 (<0.01)	
Mixed	47 (0.2)	16 (0.6)		452 (0.1)	4 (<0.01)	
White	8,922 (47.0)	1,234 (43.0)		187 (0.1)	12 (<0.01)	
Unknown	9,611 (50.7)	1,470 (51.2)		301,370 (95.4)	43,387 (99.7)	
HES linkage						
No	4,097 (21.6)	632 (22.0)	0.63	17,093 (39.2)	248,364 (78.6)	
Yes	14,867 (78.4)	2,241 (78.0)		26,418 (60.8)	67,599 (21.4)	
Travel Abroad						
No	-	-		57,850 (18.3)	8,878 (20.4)	-
Yes	-	-		2,704 (0.9)	12,643 (29.1)	
Unknown	-	-		255,409 (80.8)	21,990 (50.5)	
Requesting organisation						
GP	-	-		180,236 (57)	1,470 (3.4)	-
A&E	-	-		4,099 (1.3)	76 (0.2)	
Inpatients	-	-		21,289 (6.7)	251 (0.6)	
Outpatients	-	-		8,109 (2.6)	122 (0.3)	
Others	-	-		578 (0.2)	4 (<0.001)	
Unknown	-	-		101,652 (32.2)	41,539 (95.5)	
CCI_presence or absence						
No comorbidity	12,357 (65.2)	2,062 (71.8)	<0.001	-	-	
1 or more CHI	6,607 (34.8)	811 (28.2)		-	-	

	CPRD, 2000-2015			SGSS, 2009 -2014		
	Campylobacter **N = 18,964**	***NTS*** **N = 2,873**		***Campylobacter*** **N = 315,963**	***NTS*** **N = 43,511**	
	N (%)	**N (%)**	***P*-value**	**N (%)**	**N (%)**	***P*-value**
Smoking status						
Current	3,988 (21.0)	604 (21.0)		-	-	
Non-smoker	11,961 (63.1)	1,926 (67.0)		-	-	
Ex-smoker	1,684 (8.9)	176 (6.1)		-	-	
Missing	1,331 (7.0)	167 (5.8)		-	-	

Abbreviations and symbols: -Not applicable to the data source; *P*-value, likelihood ratio test using Pearson's Chi^2

5.4 Incidence of sequelae following *Campylobacter* and NTS infection

Incidence of reactive arthritis (ReA), irritable bowel syndrome (IBS), Guillain-Barré syndrome (GBS), ulcerative colitis (UC), Crohn's disease (CD) and rheumatoid arthritis (RA) following the selected GI infections were determined up to 12-months post-infection. For CPRD patients, both patients with or without linkage to HES were included. Recorded consultations in CPRD and diagnoses in HES were examined for a temporal association of sequelae onset following a diagnosis of either *Campylobacter* or NTS infection. For SGSS patients, the assessment of sequelae was only possible in patients with a linked record in HES. Patients with a previous diagnosis of the conditions of interest were excluded (CPRD, n =1,276; SGSS, n =5,582) (Appendix 5-2).

Less than two percent of CPRD patients (347/20,471; 1.7%, 95% C.I (1.5-1.9)) had a diagnosis recorded for sequelae, which was higher in comparison with the proportion amongst SGSS patients (1,378/353,892; 0.4%, 95% C.I (0.4-0.4)). Of the primary sequelae of interest (ReA and IBS), IBS was frequently recorded across both data sources but with a higher proportion amongst CPRD patients (73.0%, 254/347) in comparison with SGSS patients (50.0%, 678/1,397). In contrast, there was a higher proportion of the secondary

sequelae of interest diagnosed (UC, CD, RA, GBS, 48.5%, 678/1,378) amongst SGSS patients in comparison with CPRD patients (Table 5-3). The incidence of sequelae was lower in *Campylobacter* patients in comparison to NTS patients from CPRD (1.5%, 95% C.I (1.4-1.7) vs 2.7%, 95% C.I (2.1-3.4), while there were no differences amongst SGSS patients (Table 5-3).

The age and sex profiles for *Campylobacter* patients with GI infection only and those with sequelae were different for CPRD patients but similar for SGSS patients. For NTS patients, there were no differences in the age and sex profiles from both data sources (Table 5-3). *Campylobacter* patients from CPRD did not differ in age, but a higher proportion of females developed sequelae. Amongst SGSS patients, both *Campylobacter* and NTS patients with sequelae were older with a higher proportion of females than those with GI infection only. There was no social patterning across the deprivation quintiles amongst patients with sequelae in comparison with those with GI infection only across both data sources. However, this information was not available for ~20% of CPRD patients.

Recorded hospitalisation following campylobacteriosis and salmonellosis were low across both data sources. Hospitalised CPRD *Campylobacter* and NTS patients were less than 5% (GI infection only, 3.3%, 673/20,124; GI infection and sequelae, 3.7%, 13/347), while only less than one per cent of both *Campylobacter* and NTS SGSS patients required hospitalisation for their GI infection (GI infection only, 0.2%, 716/353,892; GI infection with sequelae 0.7%, 10/1,397) (Table 5-3).

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Table 5-3a *Campylobacter* patients from CPRD-linked and SGSS-linked who developed sequelae within 12-months of their GI infection in England

	CPRD, 2000-2015			SGSS, 2009-2014		
	GI infection only, N=17,564	Sequelae, N =274	*P*-value	GI Infection only, N = 309,650	Sequelae, N = 1,258	*P*-value
Age (years), mean (Sd)	44.7 (21.2)	45.6 (17.2)	0.91	44.4 (22.9)	55.1 (19.5)	<0.001
Age group (years)						
0-4	911 (5.2)	0 (0.0)	<0.001	19,684 (6.4)	9 (0.7)	
5-14	819 (4.7)	7 (2.6)		16,211 (5.2)	24 (1.9)	
15-24	1,556 (8.9)	37 (13.5)		33,220 (10.7)	115 (9.1)	
25-44	5,031 (28.6)	89 (32.5)		76,651 (24.8)	322 (25.6)	
45-64	5,868 (33.4)	98 (35.8)		95,083 (30.7)	438 (34.8)	
65+	3,379 (19.2)	43 (15.7)		68,801 (22.2)	350 (27.8)	
Sex						
Male	9,455 (53.8)	99 (36.1)	<0.001	164,439 (53.1)	528 (42.0)	<0.001
Female	8,109 (46.2)	175 (63.9)		143,851 (46.5)	728 (57.9)	
Unknown				1,360 (0.4)	2 (0.2)	
Index of multiple deprivation						
1	4,119 (23.5)	71 (25.9)	0.44	45,881 (14.8)	204 (16.2)	
2	3,565 (20.3)	62 (22.6)		56,254 (18.2)	203 (16.1)	
3	2,710 (15.4)	35 (12.7)		64,662 (20.9)	275 (21.9)	
4	2,076 (11.8)	32 (11.7)		70,982 (22.9)	312 (24.8)	
5	1,268 (7.2)	15 (5.5)		71,871 (23.2)	264 (21.0)	
missing	3,826 (21.8)	59 (21.5)		-	-	
Hospitalised						
No	17,027 (96.9)	266 (97.1)	0.90	296,038 (95.6)	1,087 (86.4)%	0.046
Yes	537 (3.1)	8 (2.9)		13,612 (4.4)	171 (13.6)	

	CPRD, 2000-2015			SGSS, 2009-2014		
	GI infection only, N=17,564	Sequelae, N =274	*P*-value	GI Infection only, N = 309,650	Sequelae, N = 1,258	*P*-value
Sequelae						
ReA	-	14 (5.1)		-	49 (3.9)	-
IBS	-	203 (74.1)		-	623 (49.5)	-
UC	-	28 (10.2)		-	310 (24.6)	-
CD	-	10 (3.6)		-	220 (17.5)	-
RA	-	11 (4.0)		-	66 (5.2)	-
GBS	-	8 (2.9)		-	15 (1.2)	-
Smoking status						
Ever smoked	5,197 (29.6)	79(28.8)	0.18	-	-	-
Never smoked	11,152 (63.5)	167 (60.9)		-	-	
Missing	1,215 (6.9)	28 (10.2)		-	-	
CCI presence or absence						
No comorbidity	174 (63.5)	11,526 (65.6)	0.46	-	-	-
1 or more CCI	100 (36.5)	6,038 (34.4)		-	-	

Abbreviations and symbols: sd – Standard deviation; CCI – Charlson comorbidity index; - not applicable to data source; Hospitalised- Patients hospitalised within 30 days of GI infection in CPRD and within 14 days of GI infection in SGSS; ; *P*-value, likelihood ratio test using Pearson's Chi^2; † events less than 5 not shown due to deductive disclosure in accordance with the ISAC protocol

Table 5-3b NTS Patients from CPRD-linked and SGSS-linked who developed sequelae within 12-months of their GI infection in England

	CPRD, 2000-2015			SGSS, 2009-2014		
	GI infection only, N=2,560	**Sequelae, N =73**	***P*-value**	**GI Infection only, N = 42,845**	**Sequelae, N = 139**	***P*-value**
Age (years), mean (sd)	36.5 (23.3)	40.3 (17.2)	0.12	32.3 (22.5)	44.7 (22.1)	<0.001
Age group (years)						
0-4	288 (10.9)	†	0.002	8,466 (19.8)	†	<0.001
5-14	359 (13.5)	5 (6.8)		4,625 (10.8)	†	
15-24	259 (9.8)	10 (13.7)		5,136 (12.0)	26 (18.7)	
25-44	684 (25.8)	22 (30.1)		9,935 (23.2)	44 (31.7)	
45-64	714 (26.9)	31 (42.5)		9,464 (22.1)	44 (31.7)	
65+	346 (13.1)	†		5,219 (12.2)	17 (12.2)	
Sex						
Male	1307 (49.3)	28 (38.4)	0.065	21,122 (49.3)	62 (44.6)	0.12
Female	1343 (50.7)	45 (61.6)		20,976 (49.0)	77 (55.4)	
Unknown				747 (1.7)	0 (0.0)	
Index of multiple deprivation						
1	570 (21.5)	17 (23.3)	0.65	8,565 (20.0)	23 (16.5)	
2	479 (18.7)	16 (21.9)		9,080 (21.2)	32 (23.0)	
3	423 (16.5)	13 (17.8)		8,533 (19.9)	29 (20.9)	
4	352 (13.8)	7 (9.6)		9,244 (21.6)	30 (21.6)	
5	233 (9.1)	4 (5.5)		7,423 (17.3)	25 (18.0)	
missing	503 (19.6)	16 (21.9)				
Hospitalised						
No	2,514 (94.9)	68 (93.2)	0.51	40,970 (95.6)	139 (100.0)	0.89
Yes	136 (5.1)	5 (6.8)		1,875 (4.4)	0 (0.0)	

	CPRD, 2000-2015			SGSS, 2009-2014		
	GI infection only, N=2,560	**Sequelae, N =73**	***P*-value**	**GI Infection only, N = 42,845**	**Sequelae, N = 139**	***P*-value**
Sequelae						
ReA	-	10 (13.7)		-	†	-
IBS	-	51 (69.9)		-	76 (54.7)	-
UC	-	†		-	46 (33.1)	-
CD	-	7 (9.6)		-	21 (15.1)	-
RA	-	†		-	†	-
GBS	-	0		-	0	-
Smoking status						
Ever smoked	1,787 (67.4)	48 (65.8)	0.66	-	-	-
Never smoked	712 (26.9)	19 (26.0)		-	-	
Missing	151 (5.7)	6 (8.2)		-	-	
CCI presence or absence						
No comorbidity	1,928 (72.8)	51 (69.9)	0.58	-	-	-
1 or more CCI	722 (27.2)	22 (30.1)		-	-	

Abbreviations and symbols: sd – Standard deviation; CCI – Charlson comorbidity index; - not applicable to data source; Hospitalised- Patients hospitalised within 30 days of GI infection in CPRD and within 14 days of GI infection in SGSS; ; *P*-value, likelihood ratio test using Pearson's Chi^2 † events less than 5 not shown due to deductive disclosure in accordance with the ISAC protocol

Table 5-4a Crude incidence rate of sequelae up to a year following *Campylobacter* infection

	CPRD, 2000 -2015					SGSS, 2009-2014				
	Events (N)	Total person time (py)	Rate per 1,000 py	[95% Conf. Interval]		Events (N)	Total person time (py)	Rate per 1,000 py	[95% Conf. Interval]	
Primary sequelae										
ReA										
1	6	1,479	4.1	1.8	9.03	0	75,695	0.0	0.0	0.0
3	9	4,386	2.1	1.1	3.94	12	75,695	0.2	0.1	0.3
6	12	8,626	1.4	0.8	2.45	22	147,999	0.2	0.1	0.2
12	14	16,710	0.8	0.5	1.41	40	281,662	0.14	0.1	0.2
IBS										
1	21	1,479	14.2	9.3	21.8	†	75,695	†	†	0.03
3	64	4,386	14.6	11.4	18.6	117	75,695	1.6	1.3	1.8
6	119	8,626	13.8	11.5	16.5	261	147,999	1.8	1.6	2.0
12	203	16,710	12.2	10.6	13.9	546	281,662	1.9	1.8	2.1
Secondary sequelae										
GBS										
1	†	1,479	†	†	†	†	75,695	†	†	†
3	†	4,386	†	†	†	†	75,695	†	†	†
6	7	8,626	0.8	0.4	1.7	5	147,999	0.03	0.00	0.1
12	7	16,710	0.4	0.2	0.9	12	281,662	0.04	0.02	0.1
Crohn's disease										
1	†	1,479	†	†	†	6	75,695	0.1	0.02	0.1
3	†	4,386	0.9	0.3	2.4	37	75,695	0.5	0.3	0.7
6	6	8,626	0.7	0.3	1.6	67	147,999	0.5	0.3	0.6
12	10	16,710	0.6	0.3	1.1	124	281,662	0.4	0.4	0.5
Ulcerative colitis										
1	†	1,479	†	†	†	5	75,695	0.1	0.01	0.1
3	†	4,386	†	†	†	50	75,695	0.7	0.5	0.8
6	17	8,626	2.0	1.2	3.2	114	147,999	0.8	0.6	0.9
12	25	16,710	1.5	1.0	2.2	211	281,662	0.8	0.7	0.9
Rheumatoid arthritis										
1	†	1,479	†	†	†	0	75,695	0.0	0.0	0.0
3	†	4,386	†	†	†	16	75,695	0.2	0.1	0.3
6	6	8,626	0.7	0.3	1.6	28	147,999	0.2	0.1	0.3
12	11	16,710	0.7	0.4	1.2	51	281,662	0.2	0.1	0.2

Abbreviations and symbols: py- person years; 95% Confidence Interval; † Events less than 5 not shown and where only one cell was affected, the next cell was also masked due to deductive disclosure in accordance with the ISAC protocol. Rate per 1,000 person years and 95% confidence interval were not calculated for events less than 5 and any other masked cell.

Table 5-4b Crude incidence rate of sequelae up to a year following NTS infection

	CPRD, 2000 - 2015					SGSS, 2009 -2014				
	Events (N)	Total person time (py)	Rate per 1,000 py	95% [Conf. Interval]		Events (N)	Total person time (py)	Rate per 1,000 py	95% [Conf. Interval]	
Primary sequelae										
ReA										
1	†	225	†	†	†	0	10,499	0.00	0.00	0.00
3	†	666	†	†	†	†	10,499	†	†	†
6	5	1,312	3.8	1.6	9.2	†	20,450	†	†	†
12	8	2,545	3.1	1.6	6.3	†	39,160	†	†	†
IBS										
1	6	225	26.6	12.0	59.3	0	10,499	0.0	0.0	0.0
3	20	666	30.0	19.4	46.5	19	10,499	1.8	1.0	2.6
6	27	1,312	20.6	14.1	30.0	35	20,450	1.7	1.1	2.3
12	51	2,545	20.0	15.2	26.4	64	39,160	1.6	1.2	2.0
Secondary sequelae										
GBS										
1	0	225	0	0	0	0	10,499	0	0	0
3	0	666	0	0	0	0	10,499	0	0	0
6	0	1,312	0	0	0	0	20,450	0	0	0
12	0	2,545	0	0	0	0	39,160	0	0	0
Crohn's disease										
1	†	225	†	†	†	†	10,499	†	†	†
3	†	666	†	†	†	†	10,499	†	†	†
6	†	1,312	†	†	†	6	20,450	0.3	0.06	0.5
12	7	2,545	2.8	1.3	5.8	15	39,160	0.4	0.2	0.6
Ulcerative colitis										
1	†	225	†	†	†	†	10,499	†	†	†
3	†	666	†	†	†	12	10,499	1.1	0.5	1.8
6	†	1,312	†	†	†	22	20,450	1.1	0.6	1.5
12	†	2,545	†	†	†	34	39,160	0.9	0.6	1.2
Rheumatoid arthritis										
1	†	225	†	†	†	0	10,499	0.00	0.00	0.00
3	†	666	†	†	†	0	10,499	0.00	0.00	0.00
6	†	1,312	†	†	†	0	20,450	0.00	0.00	0.00
12	†	2,545	†	†	†	†	39,160	†	†	†

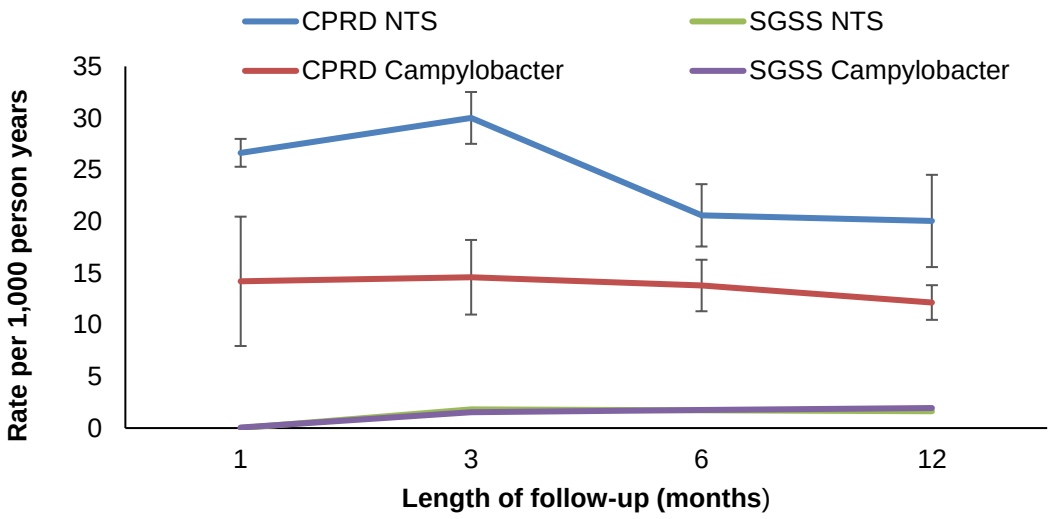
Abbreviations and symbols: py- person years; 95%[Conf. Interval] -95% Confidence Interval; † Events less than 5 not shown and where only one cell was affected, the next cell was also masked due to deductive disclosure in accordance with the ISAC protocol. Rate per 1,000 person years and 95% confidence interval were not calculated for events less than 5 and any other masked cell.

5.4.1 Time of sequelae onset - primary sequelae (IBS and ReA)

The incidence of IBS and ReA within 1-, 3-, 6-, and 12-months of follow-up were estimated to determine the period when patients were most at risk of developing sequelae.

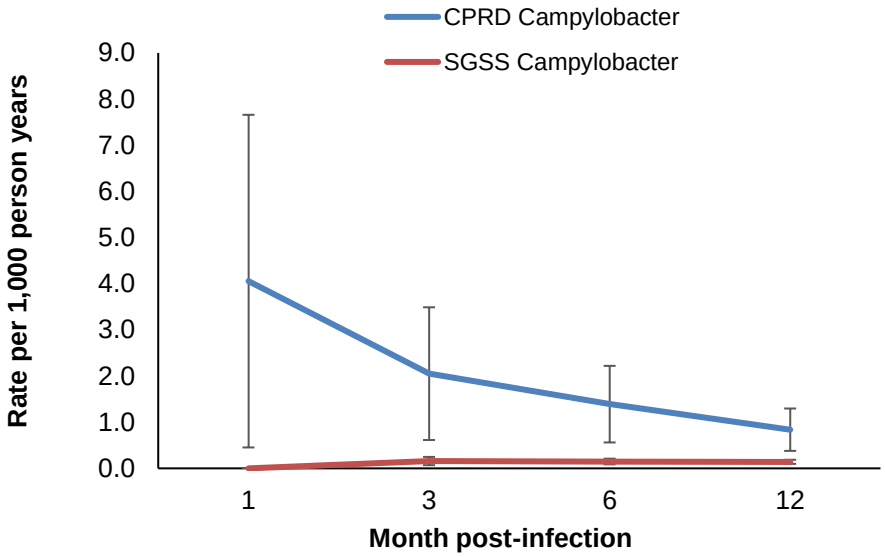
The diagnosis of IBS amongst CPRD patients was significantly higher than the recorded diagnosis for SGSS patients at each follow-up period, with the rate highest within 3-months post-infection for NTS patients (30.0 per 1,000 py, 95% C.I (19.4-46.5) (Figure 5-3, Table 5-4). This was followed by a significant decrease in the rate of onset within 6-months post-infection, with the rates remaining stable up until the end of follow up (up to 12-months post-infection) (Figure 5-9). In contrast, the rate of onset of *Campylobacter* triggered IBS remained stable over each period. In the first 3-months post-infection, the rate of *Campylobacter* triggered IBS (14.6 per 1,000 py, 95% C.I (11.4-18.6)) was approximately half the rate of NTS triggered IBS. However, the estimates for *Campylobacter* triggered IBS was more precise (Figure 5-3 and Table 5-4).

Figure 5-3 Rate of onset of IBS following *Campylobacter* and NTS infections amongst patients in CPRD, 2000-2015 and SGSS, 2009-2014



For the onset of ReA, a similar pattern of higher rates for each follow-up period amongst CPRD patients in comparison with SGSS patients was observed (Table 5-9). The rate of *Campylobacter* triggered ReA was greatest in the first month following campylobacteriosis amongst CPRD patients, although not significantly different to the rate of onset at other periods due to wide confidence intervals (Figure 5-4, Table 5-4). It was not possible to assess the rate of NTS triggered ReA within 1- and 3-months post-infection due to deductive disclosure. Within 6-, and 12-months post-infection, the rates were significantly higher than *Campylobacter* triggered ReA but less precise (Table 5-4).

Figure 5-4 Rate of onset of ReA following *Campylobacter* infection amongst patients in CPRD, 2000-2015 and SGSS, 2009-2014



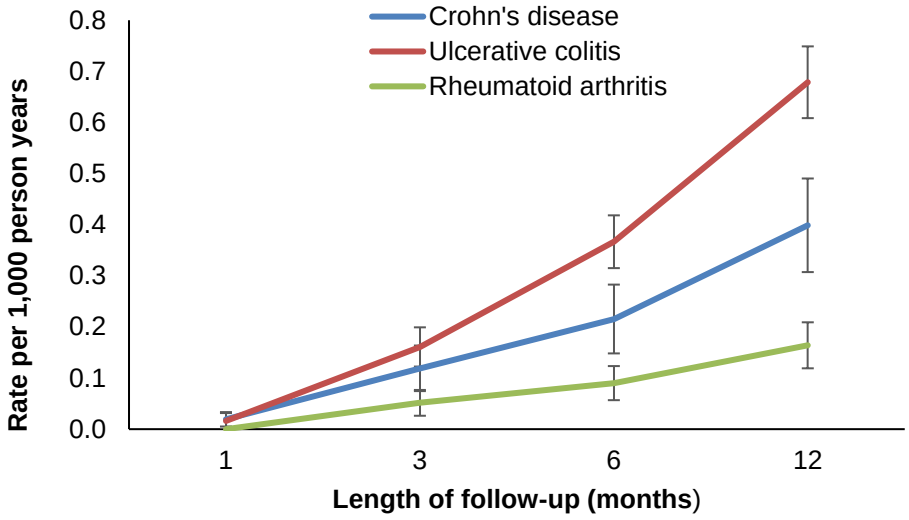
5.4.2 Time of onset - secondary sequelae CD, UC, RA, and GBS)

Figure 5-5 shows the rate of onset of CD, UC and RA within 1-, 3-, 6-, and 12-months of follow-up from the index date of infection for SGSS patients with *Campylobacte*r only, as the number of events for each time period for NTS patients from both SGSS and CPRD precluded the estimates of incidence due to deductive disclosure. The rate of onset was similar within 1- and 3-month(s) post-infection for all three sequelae. Within 6-months post-

infection, the rate of onset of UC (0.4 per 1,000 py, 95% C.I (0.3 – 0.4)) was significantly greater than the rate of onset of CD (0.2 per 1,000 py, 95% C.I (0.2 -0.3) or RA (0.1 per 1,000 py, 95% C.I (0.1 -0.2) following *Campylobacter* infection, and this pattern continued up to 12-months post-infection at an increased rate (Table 5-4).

There were no NTS-triggered GBS across both data sources. The number of patients with *Campylobacter* triggered GBS was less than five within 1-month post-infection for CPRD patients, while the number of patients within 3-months was masked to prevent deductive disclosure.

Figure 5-5 Rate of onset of UC and CD following *Campylobacter* infection amongst patients in CPRD, 2000-2015 and SGSS, 2009-2014



5.5 Secondary analysis

5.5.1 Baseline levels of sequelae – acute onset

Analysis of baseline levels of sequelae before and after infection for all patients showed there was limited ReA events amongst NTS in comparison to *Campylobacter* patients in the five years before infection across both data sources (Figures 5-6a and 5-6b). For both NTS and *Campylobacter* patients, there was a sharp rise in the incidence rate of ReA after infection, most notably in the first two months post-infection across both data sources. Levels returned to baseline rates by 11 months post-infection (Figures 5-6a and 5-6b). Additionally, for NTS patients developing ReA, there was an increased rate in the month (-1) preceding infection.

For GBS, there were no events in the five years before NTS infection across both data sources. For *Campylobacter* patients, the crude rate of GBS was less than 0.5 per 1,000 patients in the five years preceding infection across both data sources with a small peak in the incidence rate within 1-month post-infection of GBS across both data sources. (Figure 5-7a and 5-7b).

Figure 5-6a Crude rates of ReA per 1,000 *Campylobacter* and NTS patients before and after consultation date for the infection in CPRD, 2000-2015

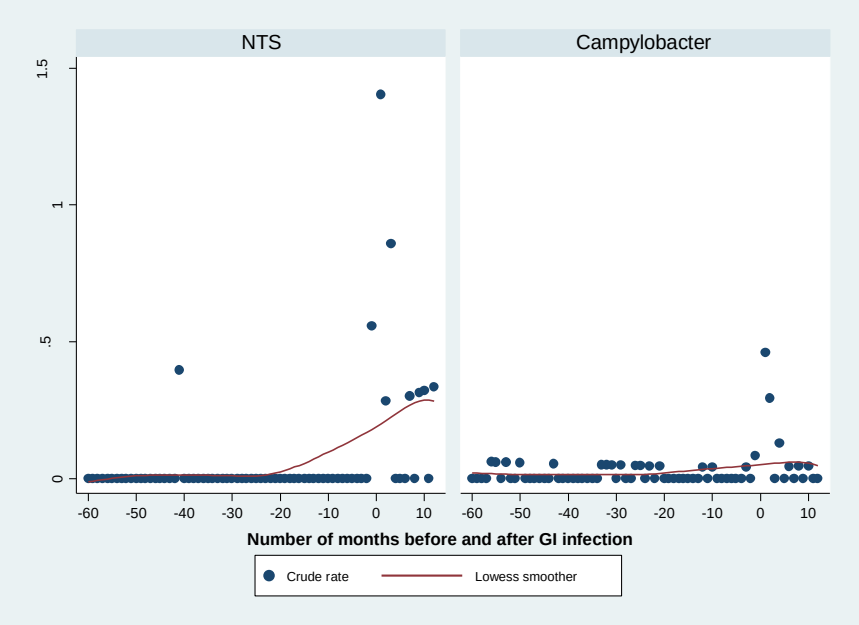


Figure 5-6b Crude rates of ReA per 1,000 *Campylobacter* and NTS patients before and after specimen date in SGSS

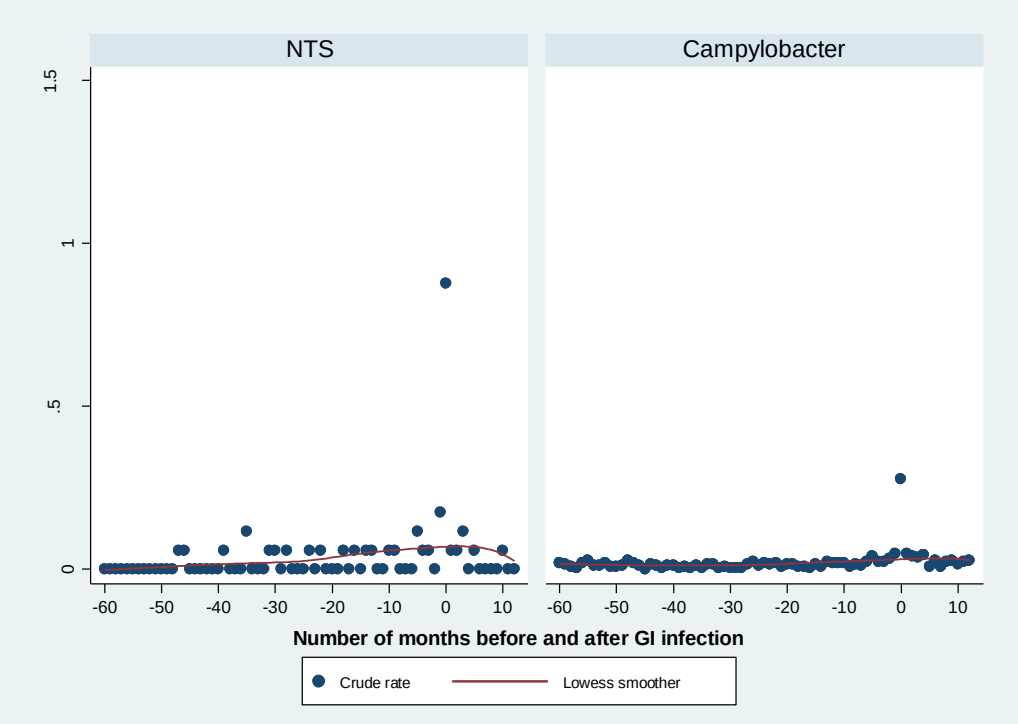


Figure 5-7a Crude rate of GBS per 1,000 *Campylobacter* patients before and after consultation date for the infection in CPRD

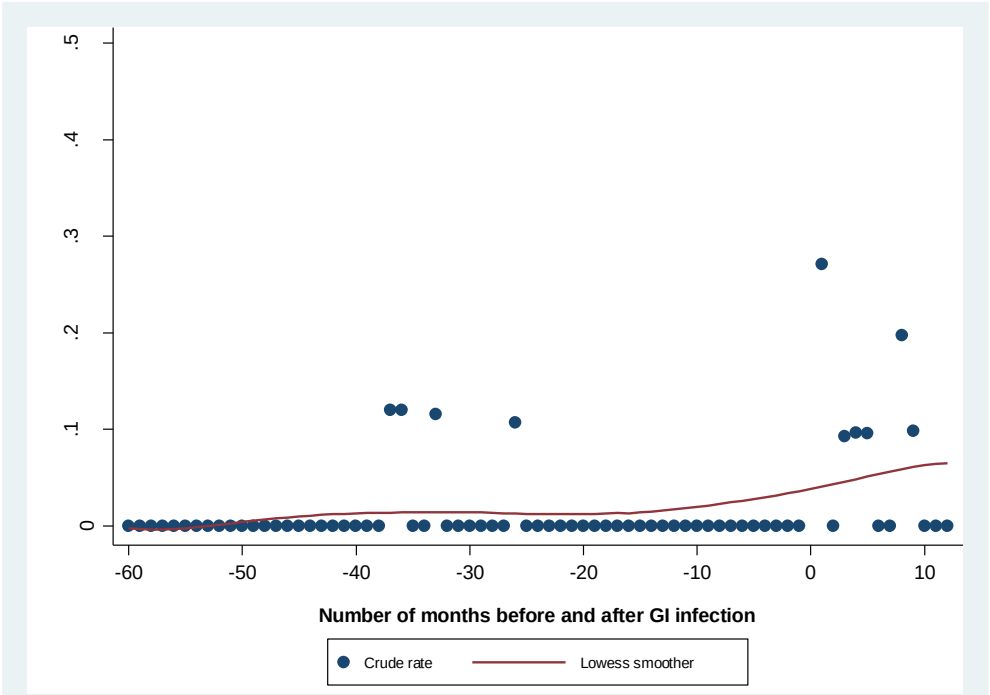
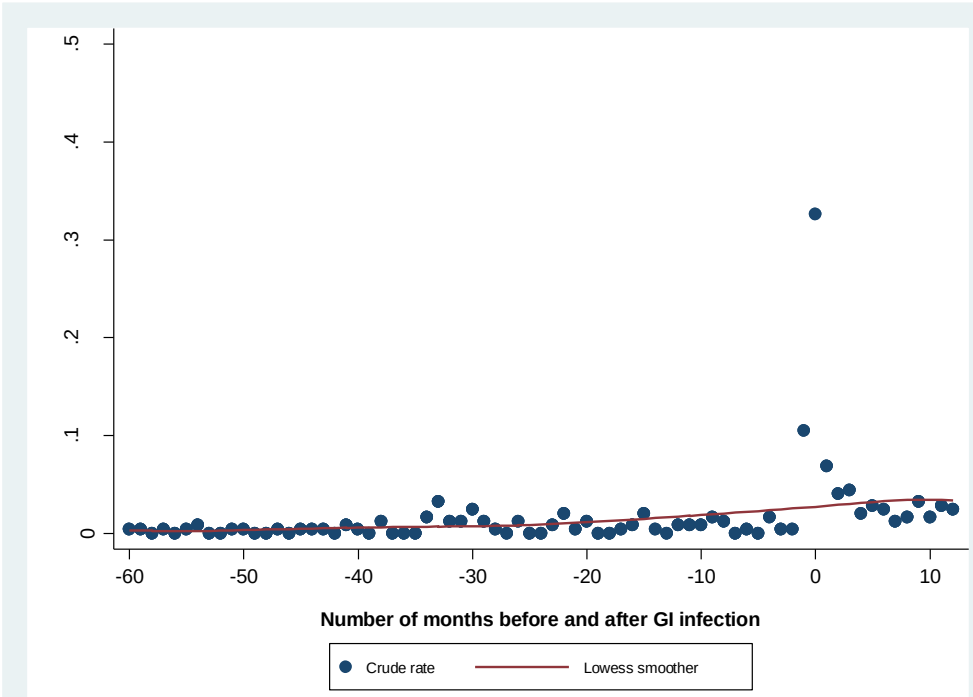


Figure 5-7b Crude rate of GBS per 1,000 *Campylobacter* patients before and after specimen date in SGSS



5.5.2 Baseline levels of sequelae – chronic onset (sequelae which are not recognised early and do not resolve within a month of onset)

For all sequelae with chronic onset, there was a sharp increase within the first-month post infection amongst SGSS patients for both *Campylobacter* and NTS infections.

For IBS, there was a higher background level of consultation in both groups of patients from CPRD in comparison to recorded diagnosis in HES amongst SGSS patients (Figures 5-8a, 5-8b and 5-8c). Although there was a slight decrease in consultation in the months preceding infection, this was immediately followed by a gradual increase in consultation rate and this increase was sustained up to 12-months post-infection for both *Campylobacter* and NTS patients from CPRD, while the rate of diagnosis in both groups of patients from SGSS patients declined from 1-month post infection (Figures 5-8a, 5-8b and 5-8c).

For the onset of UC, there was a higher background level of consultation amongst NTS patients from CPRD in the pre/post-infection period (Figures 5-9a and 5.9b). From 12-months pre-diagnosis of infection, there was a steep increase in consultations/diagnoses in NTS patients from both CPRD and SGSS, which declined from approximately 8-months post-infection. A similar pattern was observed amongst *Campylobacter* patients from both data sources, but the increase in the 12-months pre-diagnosis of infection was less pronounced (Figures 5-9a and 5.9b).

For the onset of CD, there was a decline in consultations of CD amongst NTS patients from CPRD. In contrast, there was a sharp rise in the rate of diagnosis amongst SGSS NTS patients in the 12-months before infection, reaching a peak by 6-months post-infection. The rate of consultations remained stable in the pre/post-diagnosis of infection for *Campylobacter* patients from CPRD, while for SGSS *Campylobacter* patients there was a steady increase in the diagnosis of CD both the pre/post-infection period (Figures 5-10a, and 5-10b).

For rheumatoid arthritis, the consultation rate was highest in the five years preceding infection amongst CPRD patients with a decrease in consultations both in the pre/post-infection period. In contrast, there was a steady increase in the diagnosis of RA amongst *Campylobacter* patients from SGSS while for NTS patients, the rate of diagnosis was low both in the pre/post-infection period with a small peak in the diagnosis of RA within 1-month post-infection (Figures 5-11a and 5-11b).

Figure 5-8a Crude rate of IBS per 1,000 *Campylobacter* and NTS patients before and after consultation date for the infection in CPRD

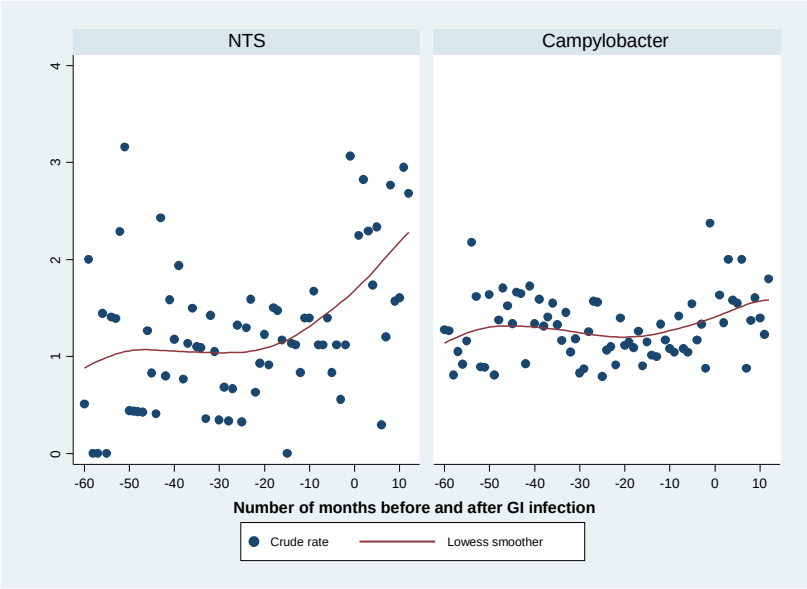


Figure 5-8b Crude rate of IBS per 1,000 *Campylobacter* and NTS patients before and after specimen date in SGSS

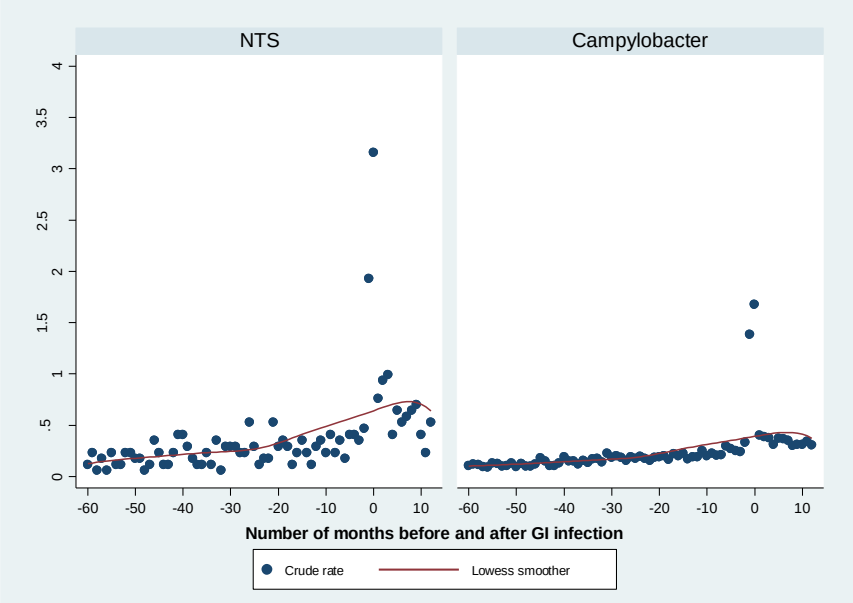


Figure 5-9a Crude rate of ulcerative colitis per 1,000 *Campylobacter* and NTS patients before and after consultation date for the infection in CPRD

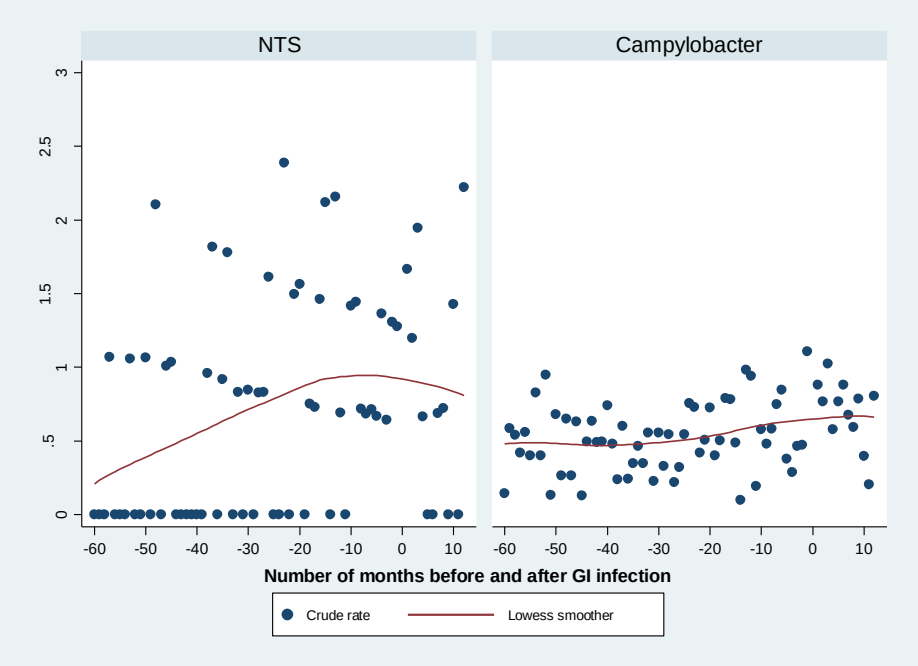


Figure 5-9b Crude rate of ulcerative colitis per 1,000 *Campylobacter* and NTS patients before and after specimen date in SGSS

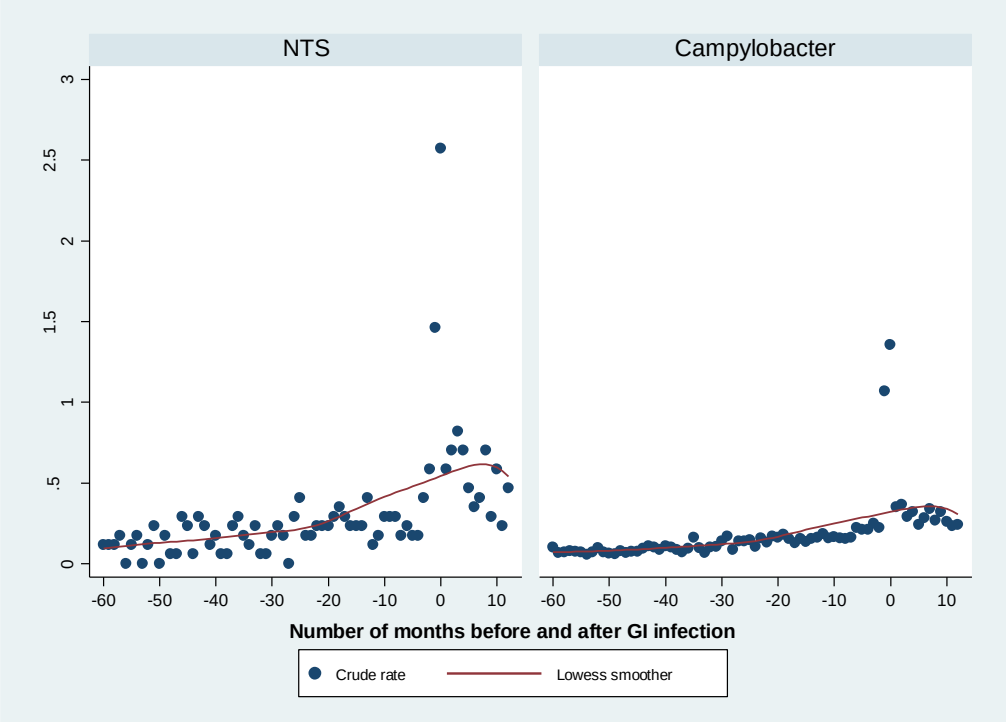


Figure 5-10a Crude rate of Crohn's disease per 1,000 *Campylobacter* and NTS patients before and after consultation date for the infection in CPRD

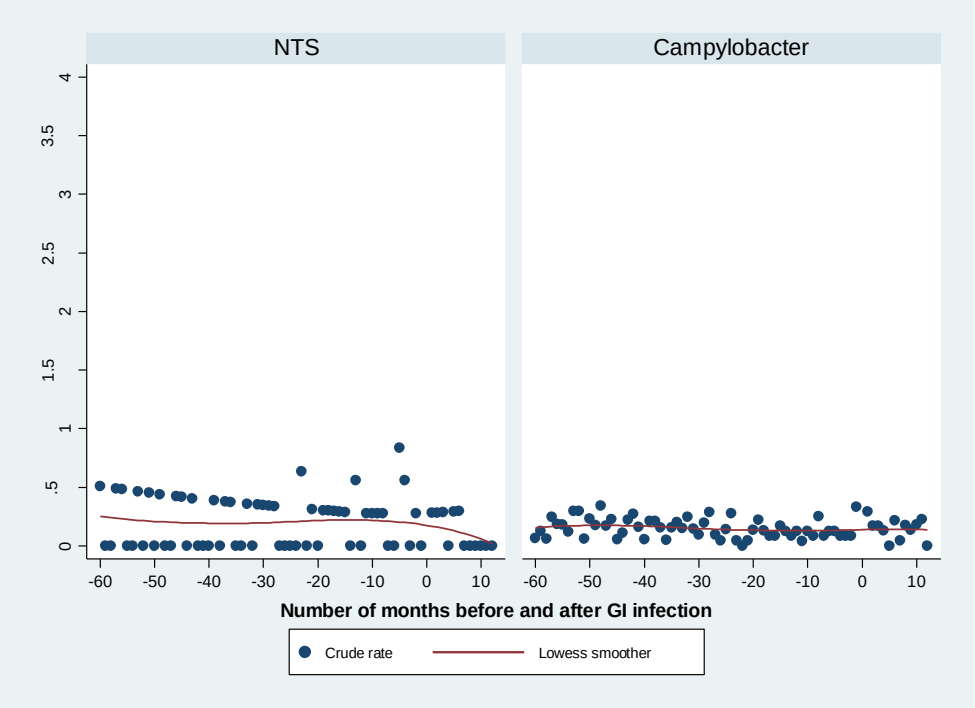


Figure 5-10b Crude rate of Crohn's disease per 1,000 *Campylobacter* and NTS patients before and after specimen date in SGSS

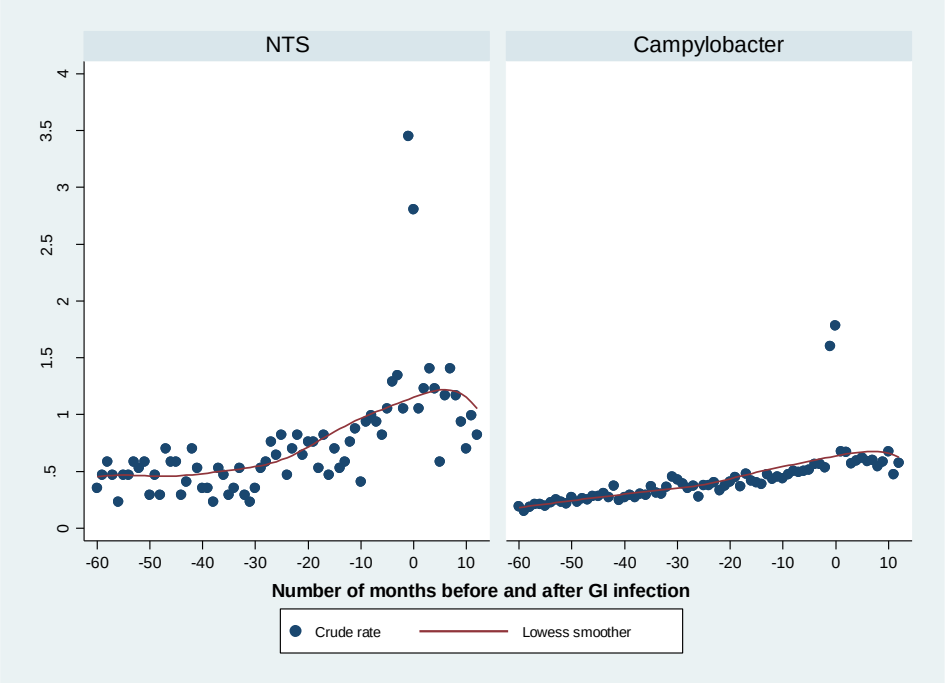


Figure 5-11a Crude rate of rheumatoid arthritis per 1,000 *Campylobacter* and NTS patients before and after consultation date for the infection in CPRD

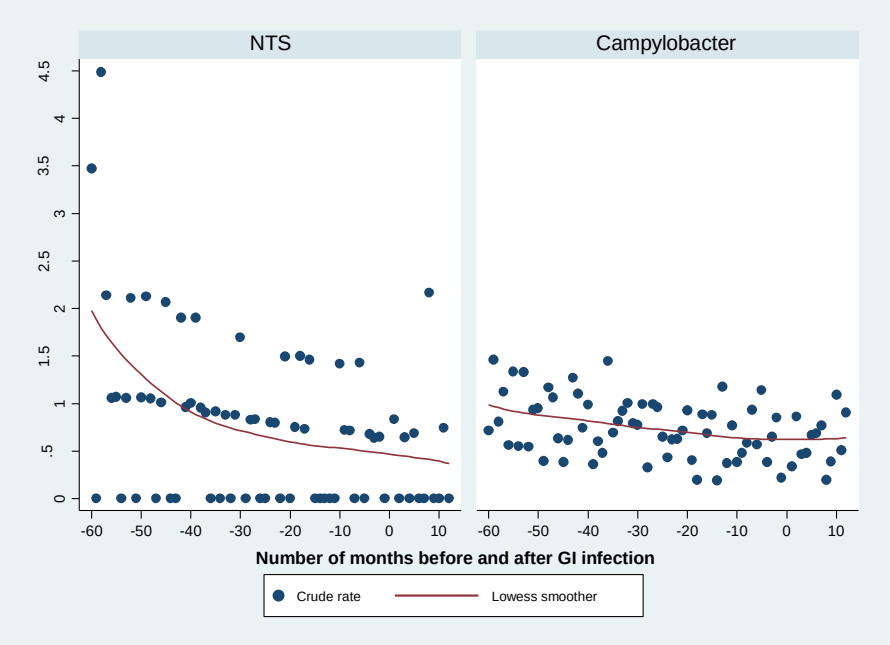
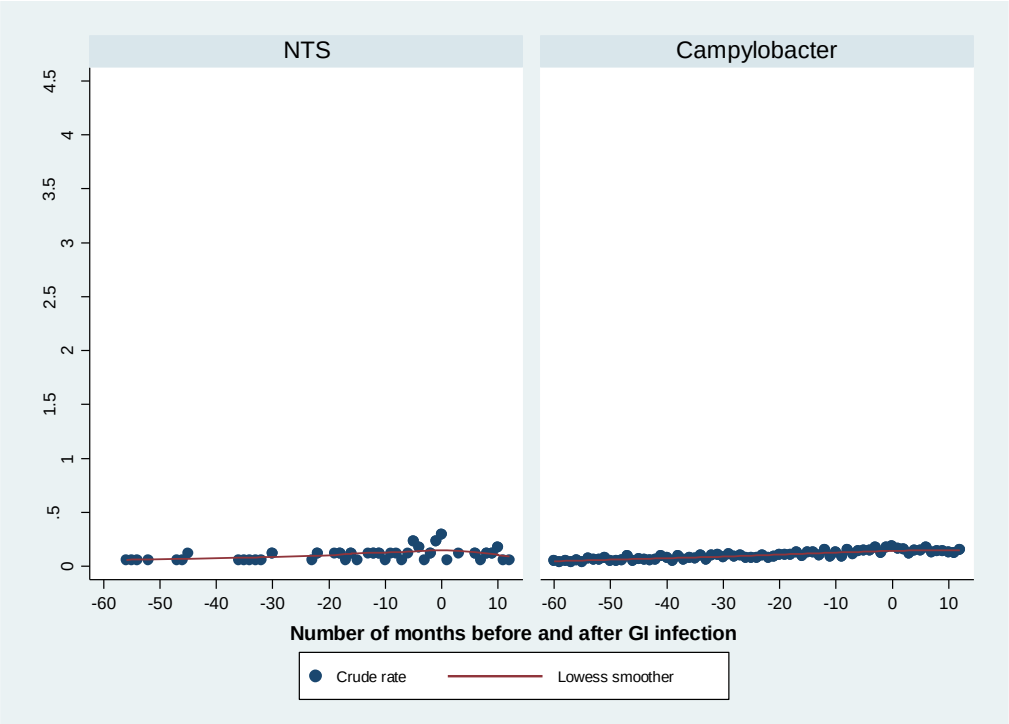


Figure 5-11b Crude rate of rheumatoid arthritis per 1,000 *Campylobacter* and NTS patients before and after consultation date for the infection in CPRD



5.6 Deaths following gastrointestinal infection amongst PHE SGSS patients

Deaths within a year of the selected GI infections were less than five amongst CPRD patients; while for SGSS patients, the selected GI infections or sequelae of interest were recorded as the cause of death in 32 patients equivalent to a death rate of 0.09 per 1,000 patients. Of the recorded deaths, most occurred in NTS patients (66%, 21/32). These patients were older (mean age 75.8 years), with a higher proportion of females (62%, 13/21) in comparison to other NTS patients from SGSS.

5.7 Discussion

5.7.1 Summary of main findings

Overall, there was a decline in the number of *Campylobacter* patients selected from CPRD in the years 2009 to 2014, with the opposite trend observed amongst SGSS patients. The fall may be due to a reduction in GP-related consultations for *Campylobacter*. All GI-related consultations declined in this period and there may not necessarily have been a decline in *Campylobacter* infections as incidence amongst patients seeking care remained relatively stable between the two iterations of IID, conducted a decade apart [1,2]. For NTS, patients from both datasets for the same period had a similar pattern of decline, which is a true reflection of the incidence of NTS for the period [3]. Notwithstanding, the characteristics of *Campylobacter* and NTS patients broadly follows what is known about the epidemiology of these infections in England. *Campylobacter* patients were older and more likely to be males, with a higher proportion of SGSS patients from regions with a higher level of rurality, while NTS infections disproportionately affect young children aged 0-4 years old and associated with foreign travel [4–6].

The overall incidence of diagnosed sequelae within 12-months post-GI infections was higher in CPRD-linked (1.7%, 347/20,471) in comparison with SGSS-linked data (0.4%, 1,378/353,892).

The mortality rate was low amongst patients from both datasets. However, where death was recorded, it was linked to NTS as the preceding infection.

A higher proportion of females developed sequelae across both data sources. NTS patients from both data sources and *Campylobacter* patients from SGSS who developed sequelae were older than their GI infection only counterparts, while there were no differences in age amongst *Campylobacter* patients with or without sequelae from CPRD. No regional differences or patterning of IMD deprivation were observed between patients with sequelae and those with GI infection only across both data sources. This is contrary to what was observed at baseline. A higher proportion of CPRD *Campylobacter* patients had a high SES, while the opposite was observed amongst SGSS *Campylobacter* patients. This may reflect inequalities in access to health services as people of a high SES are more likely to be in full-time employment with paid time off work, thus able to consult their GP during working hours in comparison with others of a low SES. Alternatively, it may be a difference in exposure or recognition of GI infection symptoms driving consultation patterns, or variations in severe consequences of GI infection [7–9].

Of the primary sequelae of interest (ReA and IBS), IBS was frequently recorded across both data sources but at a higher rate amongst CPRD sequelae patients (73.0%, 254/347) in comparison with SGSS patients with sequelae (50.0%, 678/1,397). When the rate of onset of sequelae for each GI pathogen was considered amongst CPRD patients, IBS following *Campylobacter* was greatest in the first three months post-infection (14.6 per 1,000py, 95% C.I (11.4 - 18.6)). *Campylobacter* triggered ReA was greatest within 1-month post-infection (4.1 per 1,000 py, 95% C.I 1.8 - 9.0) and within 3 months post-infection for NTS patients (7.5 per 1,000py, 95% C.I 3.1 - 18.0). However, the rates of ReA onset between the two GI pathogens were not significantly different due to wide confidence intervals for NTS patients limiting precision.

A higher proportion of patients from SGSS developed the secondary sequelae of interest (UC, CD, RA, GBS, 48.5%, 678/1,378) in comparison with CPRD patients. For the follow-up period

of up to 6-months post-infection, the rate of onset of UC following *Campylobacter* infection (0.4 per 1,000 py, 95% C.I (0.3-0.4)) was significantly greater than the rate of all other secondary sequelae onset following *Campylobacter* infection, with a sustained increase up to 12-months post-infection (0.7 per 1,000 py, 95% C.I (0.6 -0.8)). These conditions usually require specialist care in secondary care settings to confirm diagnoses. The difference between both linked SGSS and CPRD datasets may be an artefact of what it is captured in each data source.

Both ReA and GBS are acute onset sequelae with an infectious trigger as demonstrated by the limited consultations in the periods before infection. In contrast, there was a high background rate of consultation for IBS in the years leading to infection amongst patients confirming the chronic nature of the condition. It also suggests that patients can have a consultation for IBS in the absence of a confirmed GI infection.

This may be a misclassification error as patients with IBS usually present with symptoms similar to a GI infection. It is possible that some of the earlier consultations for IBS may be for a GI infection. Moreover, before a diagnosis of IBS can be confirmed, the Rome III criteria and more recently Rome IV criteria requires patients to be symptomatic both in the last three months before diagnosis and for at least 6-months following their first symptoms [10]. This may explain the high rate of onset observed within 3-months post-infection. Once patients have a diagnosis of IBS, post-infectious IBS symptoms may be prolonged for up to 10 years with varying degrees of severity and flares [11].

5.7.2 Strengths and limitations

This will be further discussed in Chapter 8. The key points are highlighted below.

Strengths

This is the first study to determine the incidence of several sequelae and other consequences in patients with *Campylobacter* and NTS infections using linked primary care, hospital, deprivation and

death records, as well as linked laboratory, hospital, deprivation and death records in England. This allowed comparisons across the different health care settings a patient with these selected GI infections are likely to encounter in England. Patients' demographics with the selected GI infections were comparable to other population studies. SGSS linked to HES allowed the direct estimation of post-infectious sequelae not possible with SGSS alone, while CPRD linked to HES allowed assessment of those who were hospitalised and the identification of patients who had a diagnosis of the sequelae of interest in a hospital before their GI infection. Consequently, misclassification bias was reduced by excluding prevalent cases from the estimates of the incidence of sequelae.

Limitations

The case definition for patients selected from CPRD-linked was based on Read codes following consultation for *Campylobacter* or NTS infections. This is subjective to GP behaviour during the consultation as not all GPs follow the stipulated guidelines in requesting stool culture from patients presenting with symptoms of gastroenteritis. GPs are more likely to request a stool culture if the patient reported foreign travel or have severe symptoms such as bloody diarrhoea or prolonged diarrhoea [12,13]. It was not possible to stratify patients by severity of symptoms as these are usually recorded within the free text field not available to researchers.

Further, where stool culture is requested, not all results are systematically recorded as previously described (section 4.7.1) [13,14]. This may have introduced selection bias in the sampling of patients who were selected based on having a positive test for either *Campylobacter* or NTS infection. Moreover, not all samples tested will yield a pathogen, and negative results are not recorded in SGSS, and changes in sampling methods can also influence what is detected. However, between the two iterations of the IID studies, the proportion of samples yielding positive results for *Campylobacter* increased as a result of the introduction of PCR. Conversely, NTS infections declined as a consequence of industry-led control measures to reduce infections [15 16]. Further, the study was

conducted at a time when GP consultations for GI infections had halved (2008/2009 onwards) this may explain the apparent decline in patients with *Campylobacter* infection selected from CPRD in comparison to those from SGSS-linked [17].

Comparing characteristics of patients in SGSS-linked with CPRD-linked emphasises the need to link all three datasets. Only a quarter of patients from SGSS had a record in HES to enable linkage. Hence, the incidence of sequelae was only quantified amongst patients with a diagnosis in HES. Consequently, sequelae commonly diagnosed within primary care such as IBS and ReA may be underestimated, while those diagnosed and managed within secondary care such as UC may be overestimated using this data source as demonstrated in the findings.

IMD was only available for patients who consented to linkage in CPRD; this may have contributed to the observed differences in SES patterning of *Campylobacter* patients between the two data sources.

Ethnicity was poorly recorded in the SGSS-linked data with improvements in CPRD-linked data. However, 45% of CPRD-linked patients did not have ethnicity recorded. White ethnic group was the most reported suggesting recording of ethnicity is not missing at random.

5.7.3 Conclusion

The demography of patients selected from CPRD with selected GI infections is consistent with patients' characteristics in SGSS in England except for their SES. *Campylobacter* patients in CPRD are likely to have a high SES, with the reverse for SGSS patients. IBS was the most common sequelae following *Campylobacter* and NTS infection and was frequently recorded in the primary care data. ReA and GBS are sequelae of acute onset, while IBS has an insidious onset. Incidence of UC and CD following *Campylobacter* or NTS infection was low in both primary and secondary care settings. However, it was slightly higher in the SGSS-linked data. There was limited evidence of the selected GI infections triggering RA. Although the rate of sequelae was significantly higher

in NTS patients, the estimates may not be reliable due to small numbers, as such only *Campylobacter* patients were considered in a logistic regression model to assess the factors associated with sequelae onset in Chapter 6.

5.8 References

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Chapter 6

Risk factors associated with the onset of sequelae following *Campylobacter* infection

6.1 Overview

This chapter presents the results of the hypothesis testing to determine if treatment of *Campylobacter* infection with antibiotics or long-term usage of PPI are associated with the development of sequelae in these patients. Specifically, the proportion of patients taking or not taking the medications of interest are presented along with the risk estimates from the logistic regression model and multivariate analyses using predefined covariates (age, sex, CCI, smoking, and IMD-quintile). Methods and statistical analyses were outlined in Chapter 4. The baseline characteristics of patients, including the covariates and crude incidence rate of each sequela, have already been described in Chapter 5.

Objective C: *To determine the risk factors associated with sequelae amongst individuals diagnosed with Campylobacter who may or may not have used antibiotics (macrolides, quinolones or cephalosporins) or PPI before and after their infection.*

6.2 Study population

The study was only powered to test the hypothesis on *Campylobacter* patients (n=18,960). Patients with a previous diagnosis of the conditions of interest (n = 1,122) were excluded to prevent any dilution effect in the estimates of the odds ratio. Patients with multiple sequelae (n = 4) were also excluded as it would not be possible to determine which of the sequela occurred as a result of

taking antibiotics or PPI. In total, 17,834 *Campylobacter* patients were included in testing the association between sequelae onset and treatment with antibiotics; for the association between sequelae onset and previous exposure to PPI, it was restricted to patients aged 18 and over (n= 15,809).

6.3 Patients exposure to medications

6.3.1 Patients prescribed antibiotics

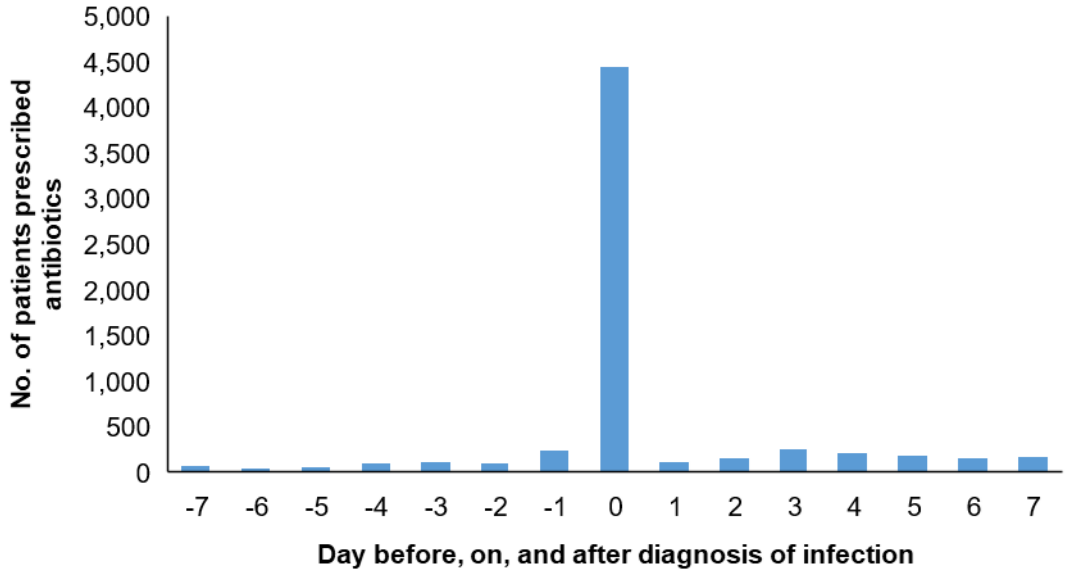
Over a third of patients (36.5%, 6,500/17,834) in the cohort had a prescription for antibiotics in the seven days before, on, and seven days after diagnosis of *Campylobacter* infection (Table 6-1). Most of these patients (68.4%, 4,446/6,500) had a prescription recorded on the same date of diagnosis of infection (Fig 6-1), with quinolones as the frequently recorded prescription (61.1, 3974/6,500). Patients with antibiotics prescription were marginally younger with no difference in sex distribution, smoking and comorbidity status in comparison to patients without a prescription for the antibiotics of interest (Table 6-1).

Table 6-1 Comparison of patients with or without prescription for antibiotics in the seven days before, on, and after diagnosis of *Campylobacter* infection

	Antibiotics prescription N =6,500		No antibiotics prescription, N = 11,334		
	N	%	N	%	*P*-value
Age mean (SD)	43.2 (21.1)		45.5 (21.2)		<0.001
Age group (years)					
0-4	438	6.7	473	4.2	<0.001
5-14	324	5.0	502	4.4	
15-24	528	8.1	1,064	9.4	
25-44	1,902	29.3	3,218	28.4	
45-64	2,242	34.5	3,722	32.8	
65+	1,066	16.4	2,355	20.8	
Sex					
Male	3,420	52.6	6,132	54.1	0.055
Female	3,080	47.4	5,202	45.9	
Prescription event					
None	-	-	11,334	100.0	-
up to 7 days before infection	779	12.0	-	-	
Day 0	4,446	68.4	-	-	
up to 7 days after infection	1,275	19.6	-	-	
Antibiotics class					
Quinolones	3,974	61.1	-	-	
Macrolides	2,640	40.6	-	-	
Cephalosporins	66	10.2	-	-	
Smoking status					
Current	1,384	21.3	2,320	20.5	0.20
Ex-smoker	547	8.4	1,024	9.0	
Missing & no smoker	4,569	70.3	7,990	70.5	
CCI presence or absence					
No comorbidity	4,317	66.4	7,380	65.1	0.078
1 or more CCI	2,183	33.6	3,954	34.9	
Any sequelae					
No	6,395	98.4	11,165	98.5	0.52
Yes	105	1.6	169	1.5	

- Not applicable

Figure 6-1 Patients with antibiotics prescription in the seven days before, on and after diagnosis of *Campylobacter* infection



6.3.2 Patients prescribed proton pump inhibitors

Approximately a quarter of patients (26.0%, 4,115/15,809) in the cohort had a prescription for PPI up to one year before infection (Table 6-2). These patients all had a prescription at 12-months before infection, with a gradual decline in the number of patients receiving prescriptions in the 3-months before infection (86%, 3,538). Patients with prescriptions for PPI were older (59.0 years old vs 46.2 years old), had a CCI of 1 or more (55.9% vs 29.9%), and a higher proportion developed sequelae (any sequelae 2.2% vs 1.5%; IBS 1.6% vs 1.1%) in comparison with patients with no PPI prescription (Table 6-1). Omeprazole was the frequently prescribed PPI with some patients receiving prescriptions of up to 50 PPI (median 6, IQR 2, 10) in the 12 months before the onset of infection.

Table 6-2 Comparison of patients with or without prescription for PPI within 12 months before the diagnosis of *Campylobacter* infection

	PPI Prescription, N = 4,115		No PPI prescription, N = 11,694		
	N	%	N	%	*P*-value
Age mean (SD)	59.0 (15.3)		46.2 (16.7)		<0.001
Age group (years)					
18-44	727	17.7	5,694	48.7	<0.001
45-64	1,776	43.2	4,188	35.8	
65 +	1,612	39.2	1,809	15.5	
Sex					
Male	2,129	51.7	6,184	52.9	0.21
Female	1,986	48.3	5,510	47.1	
Prescription event					
PPI up to 3months before*	3,538	86.0	-	-	
PPI up to 6months before	3,821	92.9	-	-	
PPI up to 9 months before	3,980	96.7	-	-	
PPI up to 12 months before	4,115	100.0	-	-	
Smoking status					
Current	1,100	26.7	2,557	21.9	
Ex-smoker	559	13.6	1,011	8.6	
Missing & none	2,456	59.7	8,126	69.5	
CCI presence or absence					
No comorbidity	1,813	44.1	8,194	70.1	<0.001
1 or more CCI	2,302	55.9	3,500	29.9	
Any sequelae					
No	4,026	97.8	11,517	98.5	0.007
Yes	89	2.2	177	1.5	
IBS					
No	4,048	98.4	11,564	98.9	0.004
Yes	67	1.6	130	1.1	

*Prescription in the months before the diagnosis of infection; - not applicable

6.4 Association between medications and sequelae onset

There was no association between antibiotics and the onset of each of the primary sequelae of interest as evidenced by the unadjusted and adjusted odds ratio (Table 6-3).

Table 6-3 Summary of the logistic regression model for the association of antibiotics and PPI with sequelae onset in *Campylobacter* patients

Antibiotics, N =17,834

Outcome	N	OR ‡	[Conf. Interval][3]		*P*-value	aOR‡‡	[95% Conf. Interval][3]		*P*-value
IBS[1]	203	1.04	0.78	1.39	0.768	1.02	0.77	1.36	0.893
ReA[1]	14	1.74	0.61	4.98	0.298	1.8	0.63	5.13	0.274
UC	33	1.51	0.57	4.02	0.275	1.57	0.59	4.17	0.237
CD	10	0.44	0.06	3.34	0.293	0.43	0.06	3.3	0.289
RA	11	2.09	0.44	9.96	0.223	2.27	0.47	10.89	0.176

Abbreviations and symbols: [1]Primary outcomes; ‡ unadjusted odds ratio; ‡‡Adjusted odds ratio (adjusted for age and sex); [3][95% confidence interval] for primary outcomes; *P*-value likelihood ratio test.

The effect between the class of antibiotics prescribed and the onset of sequelae was only assessed for the onset of IBS only due to the small numbers of patients with other forms of sequelae. Patients prescribed cephalosporins had a 4-fold risk of onset of IBS (OR 4.2, 95% C.I (1.2 -13.6), *P*=0.016), when the risk was adjusted using the predefined covariates (age, sex, CCI and smoking status) there was a slight reduction in effect size, while females taking antibiotics had a moderate risk of IBS (aOR 3.6, 95% C.I (1.1 – 11.7) (Table 6-4). Nonetheless, the wide confidence intervals in both unadjusted and adjusted models suggest the observed effect may be due to chance as less than one per cent of patients (0.4%, 66/17,834) in the cohort received cephalosporins (Table 6-4).

Table 6-4 Multivariate logistic regression model for the effect of the prescribed class of antibiotics on the onset of IBS in *Campylobacter* patients

Patients (N) = 17,834

IBS	OR‡	[95% Conf. Interval]		*P*-value	aOR‡‡	[95% Conf. Interval]		*P*-value
Antibiotics								
No antibiotics	Referent	-	-	-	Referent	-	-	-
Quinolones	1.2	0.9	1.6	0.328	1.1	0.8	1.5	0.731
Macrolides	0.8	0.5	1.2	0.264	0.9	0.6	1.4	0.588
Cephalosporins	4.2	1.3	13.7	0.016	3.6	1.1	11.7	0.033
Age (years)					1.0	1.0	1.0	0.1
Sex								
Male	Referent	-	-	-	Referent	-	-	-
Female	-	-	-	-	2.6	1.9	3.5	<0.001

‡ Unadjusted odds ratio; ‡‡Adjusted odds ratio (adjusted for age, sex, smoking status and CCI); Model *P*-value: likelihood ratio test for unadjusted odds ratio, *P*=0.079; adjusted odds ratio *P* <0.001

For patients with a PPI prescription, there was an elevated risk in the onset of IBS (OR 1.5 95% CI 1.1-2-0, *P*=0.011) which was further elevated in the multivariate analysis with retained significance (aOR 2.1 95% CI 1.5-2.9, *P*<0.001) (Table 6-5). No real effect was observed for the secondary sequelae following the prescription of PPI amongst *Campylobacter* patients (Table 6-5).

Table 6-5 Summary of the logistic regression model for the association of prescription for PPI within 12 months before sequelae onset in *Campylobacter* patients, 2000-2015

Proton pump inhibitors, N = 15,806

Outcome	N	OR ‡	[Conf. Interval] [3]		*P*-value	aOR‡‡	[99% Conf. Interval] [3]		*P*-value
IBS[1]	197	1.5	1.1	2.0	0.011	2.1	1.5	2.9	<0.001
ReA[1]	14	0.8	0.2	2.8	0.695	0.8	0.2	3.1	0.758
UC	27	1.7	0.6	4.7	0.197	1.5	0.5	4.5	0.333
RA	11	1.6	0.3	8.2	0.439	1.0	0.2	5.5	0.978

Abbreviations and symbols: [1]Primary outcomes; ‡ unadjusted odds ratio; ‡‡Adjusted odds ratio (adjusted for age and sex); [3][99% confidence interval] for secondary outcomes to limit type I error; *P*-value likelihood ratio test. Crohn's disease was not included in the logistic regression for association with PPI as only nine patients met the criteria.

The influence of other covariates on the effect of IBS onset in *Campylobacter* patients taking PPI was analysed by including the smoking status of patients and the presence of comorbidities in addition to age and sex in a multivariate analysis (Table 6-6). There was no change in the size or direction of effect on the risk of IBS and the use of PPI amongst *Campylobacter* patients as the smoking status, or existence of comorbidities in patients did not affect the onset of IBS. The elevated risk observed in females also remained at a similar level, while those aged 65 and above had the lowest risk of developing IBS as the effect on younger patients remained (Table 6-6).

Table 6-6 Multivariate logistic regression model for the effect of prescribed proton pump inhibitors up to one year before infection amongst *Campylobacter* patients

Irritable bowel syndrome and PPI prescription (adjusted for age, sex, smoking status and Charlson comorbidity index), model *P*-value, *P* <0.001

		OR‡	**[95% Conf. Interval]**		***P*-value**
PPI		2.0	1.4	2.7	<0.001
Age group (years)					
18-44	Referent				
45-64		0.7	0.5	0.9	0.009
65+		0.3	0.2	0.5	<0.001
Sex					
Male	Referent				
Female		2.5	1.9	3.4	<0.001
Smoking status					
Missing and none	Referent				
Current		0.8	0.6	1.2	0.237
Ex-smoker		1.1	0.7	1.7	0.778
CCI					
None	Referent				
1 or more		1.0	0.7	1.3	0.74

Abbreviations and symbols: CCI Charlson Comorbidity Index; ‡Unadjusted odds ratio**;** 95% Confidence Interval; *P*-value likelihood ratio test.

To determine which age groups below 65 years were at a greater risk of IBS onset, age was re-categorised (Ref age group (18-24), 25-44, 45-64, and 65+) and the multivariate logistic regression was fitted with a test for trend performed on the age categories and their interactions using the STATA's contrast command as previously described (4.8.2). Those aged 18-44 years had the greatest risk of IBS onset. However, there was no significant trend across all the age groups (Appendix 6-1).

6.5 Sensitivity and secondary analysis

6.5.1 Sensitivity analysis

The presence of interactions between all predictors (PPI, age, sex, smoking status, and comorbidity), and the onset of IBS were assessed to determine if a change in the predictor in the model affected the onset of IBS. There was no evidence of any interaction with any of the covariates as $P > 0.05$ (Table 6-7).

Table 6-7 Assessment of interactions between PPI and covariates amongst *Campylobacter* patients with IBS

Patients included in model, n = 15,806

Factor	aOR# for IBS[1]	[95% Conf. Interval]		*P*-value
Age	1.0	1.0	1.0	0.984
Sex				
Males	Referent			
Females	1.2	0.6	2.2	0.656
Smoking status				
Non-smokers/missing	Referent			
Current	0.9	0.4	1.9	0.776
Ex-smokers	0.9	0.3	2.8	0.741
CCI				
None	Referent			
1 or more	1.3	0.5	0.7	2.35

Abbreviations and symbols: CCI - Charlson comorbidity index; #Adjusted odds ratio (adjusted for age, sex, smoking status and CCI); IBS[1]- 197 patients developed IBS; 95% Confidence Interval; *P*-value likelihood ratio test

To determine if there were differences between patient's SES and the onset of IBS amongst patients using PPI; patient's IMD-quintile was included in the logistic regression model for patients with a linked record only (n =12, 358). Although the PPI-IBS effect was slightly attenuated (aOR 2.0, 95% C.I (1.4-3.0) and PPI appeared to have a protective effect amongst patients with a lower SES, the observed effect remained significant when a test for trend was applied to the fitted model (Appendix 6-2).

6.5.2 Secondary analysis

To further assess the relationship between the use of PPI in *Campylobacter* patients and the onset of PPI; the follow-up period between infection and sequelae onset and the total number of PPI prescribed to patients were considered in a secondary analysis (Table 6-8 and Table 6-9).

Table 6-8 Multivariate analysis of the effect of PPI on IBS onset with different follow-up period amongst *Campylobacter* patients

	Patients with IBS	aOR#	[95% Conf. Interval]		*P*-value
Follow-up period [1]					
Up to 1 month	30	2.31	1.03	5.16	0.01
Up to 3 months	48	2.88	1.55	5.34	<0.001
Up to 6 months	68	2.37	1.4	4.02	<0.001
Up to 12 months	109	1.48	0.95	2.3	<0.001

Abbreviations and symbols: #adjusted odds ratio (adjusted for age and sex only); [1] - time of onset post-infection; *P*-value likelihood ratio test

There was an increase in the risk of the onset of IBS between 1- and 3-months post-infection. Although the risk declined from 6 months onwards, a significant association remained (Table 6-8).

Table 6-9 Multivariate analysis of the effect of PPI on IBS onset using the number of PPI prescriptions as a categorical variable amongst *Campylobacter* patients

	Patients with IBS	aOR#	[95% Conf. Interval]		*P*-value
Total PPI					
0	130	Referent			
5-9	34	2.1	1.4	3.0	<0.001
6-10	18	2.0	1.2	3.3	0.01
>10	15	2.5	1.4	4.4	<0.001
Age	197	1.0	1.0	1.0	<0.001
Sex	197	2.5	1.9	3.4	<0.001

Abbreviations and symbols: #adjusted odds ratio (adjusted for age and sex only); 1 - time of onset post-infection; P-value likelihood ratio test

When the total number of PPI prescriptions was used in place of the presence or absence of PPI as the independent variable, the risk of IBS onset appeared to be greater with those who had more than 10 PPI prescribed within a year before infection (OR 2.5, 95% CI (1.4-4.4), *P*<0.001) (Table 6-9). However, applying a test for trend on the fitted model by comparing each category of the

total number of prescriptions vs none demonstrated that the risk was not significantly different to the risk for those with less than 10 PPI prescriptions (P<0.001) (Appendix 6-3).

6.6 Discussion

6.6.1 Summary of main findings

The relative risk of developing IBS following *Campylobacter* infection increased by 50% (OR 1.5, 95% CI 1.1-2.0) amongst patients with prior long-term PPI (1.6%) in comparison to patients without PPI (1.1.%). Adjusting for potential confounders, patients with a prescription for PPI had a 2-fold likelihood of developing IBS following their *Campylobacter* infection (aOR 2.1, 95% C.I 1.5-2.9, P<0.001), with female sex (OR 2.5, 95% C.I 1.9-3.4, P<0.001) as an independent risk factor. Hence the absolute risk of developing IBS amongst *Campylobacter* patients doubles if patients are on prior long-term PPI (1.6% to 3.2%). This is a novel finding which is supported by a plausible biological mechanism.

PPI inhibits H+/K +-ATPase activity in the stomach by blocking all three proton pump channels leading to impaired gastric acid secretion, thereby increasing the pH to a level (1.4 to 4) that favours pathogenic bacteria [1,2]. *Campylobacter* infection can disrupt the microbiota composition and function through mucosal invasion and impaired neuromuscular and immune regulation. When this occurs following pH disruptions, the passage of pathogens into the intestines is aided, which can trigger IBS [2,3].

Females with prior PPI prescription with antecedent *Campylobacter* infection were 2.5 times more likely to develop IBS (absolute risk increases from 1.6% to 4%). This reflects their overall increased propensity for the development of IBS symptoms. Many functional disorders are more common among females and could be partially attributed to gender-specific factors such as circulating female sex hormones and changes in rectal sensitivity during menstrual cycles. Furthermore, the

increased prevalence of psychological symptoms of anxiety, depression and somatisation in females are also modifiable factors associated with IBS [4]. This interactive model of biology and psychology in the onset of IBS is now well established [5–8]. Infection may trigger the initial symptoms, while cognition, behaviour and emotions may prolong and maintain them over time [5].

A recent meta-analysis reported an elevated risk of the same magnitude for women (OR 2.2, 95% C.I 1.6-3.1) in the onset of IBS following infectious gastroenteritis, and also found younger age to be an independent risk factor. Further, previous studies on the prevalence of IBS have demonstrated it is more pronounced in younger age as over 50% of patients present with their first symptoms by age 35, while prevalence is 25% lower in people aged 50, while the onset of IBS in females has been linked to antecedent *Campylobacter* infection [9,10]. Although, there was a higher proportion of patients aged 65 and above amongst PPI users in comparison to non-PPI users (39.2% vs 15.5%), their risk of IBS may be reduced due to earlier exposure in life that may not have been captured in CPRD or HES due to varying degree of clearance, relapse or flares.

Secondary analyses revealed the risk of IBS was highest in the first 3-months after diagnosis of *Campylobacter* infection (aOR 2.9, 95% C.I 1.4-4.0, $P<0.001$). The rate of onset of IBS was also greatest within this period, as shown in Chapter 5 (section 5.4.1). Although, there was limited scope to measure a dose-response relationship, the proxy measure for this was the total number of PPI prescriptions received in the year leading up to *Campylobacter* infection. Including this in the model did not influence the level of risk. Instead, it only indicated that younger female *Campylobacter* patients on PPI irrespective of the number taken had an elevated risk of IBS. Moreover, there were no significant observed interactions between the covariates and the onset of IBS. These confirm the increased risk of IBS amongst PPI users with antecedent *Campylobacter* infection.

Restricting the analysis to patients with linked IMD quintile revealed that patients living in less privileged areas (IMD-3 and IMD-4) were less likely to develop IBS if they had a prescription for PPI. This supports existing evidence of a social patterning of IBS, as the risk of onset is elevated

amongst those with a high SES which is indicative of a lifestyle influence. Stress, anxiety, and increased somatisation have been linked to the onset of IBS. It is perceived that those in professional or managerial roles may have a high degree of stress. On the contrary, those of a lower SES usually have worse health outcomes with increased life stressors [11]. Alternatively, some studies report that a third of infection triggered IBS is linked to foreign travel, which may occur more frequently amongst those of a high SES [12]. Others suggest that being in a higher SES group during childhood increases the risk of IBS as early exposure to GI pathogens is low in this group and adaptive immunity is usually developed to pathogens such as *Campylobacter* if there is exposure in early life [13]. Nonetheless, the SES of patients in the cohort is also a direct reflection of access to healthcare as there was a higher proportion of patients of a high SES at baseline (section 5.5.2).

There was no association with antibiotics and the onset of any of the studied sequelae. In contrast, a meta-analysis reported antibiotics treatment of GI infections as an independent risk factor in the onset of IBS following infectious IBS (OR 1.7, 95% C.I 1.20-2.37) [4]. However, they included multiple types of GI pathogens – bacteria, viruses, parasites and protozoa with prevalence highest amongst patients with a parasitic infection [4].

Over a third of patients in this study were prescribed antibiotics in the seven days before and after diagnosis of infection, with over half of them (68.4%), equivalent to a quarter of patients in the cohort receiving antibiotic prescription on the same day as their diagnosis for *Campylobacter* infection. This is against the stipulated guidelines where treatment of infection is only indicated in patients who are systemically unwell [13]. Only a small proportion of the cohort appear to fit this category as less than 5% of patients were hospitalised (section 5.5.4). Quinolones were the most frequently prescribed class of antibiotics to patients in the cohort. It is a broad-spectrum antibiotic which is not recommended for empirical treatment of *Campylobacter* infection due to an increase in antimicrobial resistance, and recurrent urinary tract infections [14]. Clarithromycin, a macrolide is

instead the recommended antibiotic when treatment is indicated for *Campylobacter* infection [14]. Less than half of the patients prescribed antibiotics received a macrolide.

6.6.2 Strengths and limitations

This is discussed further in Chapter 8. The key points are highlighted below.

Strengths

This is the first population study to assess the risk of modifiable risk factors in the onset of sequelae amongst patients with *Campylobacter* infection. Excluding patients with a history of the conditions of interest implies that effect estimates are not overestimated as only incident cases were included and not prevalent cases. The large sample size implies that estimates are precise, internally valid as evidenced by the association of sequelae with the exposure of interest, and any observed effect was not due to chance. Using a representative population for England implies that results are generalisable for the whole of England.

Limitations

Possible indications for PPI prescription were not included in the regression model. However, the CCI was used as a measure of pre-existing conditions, and this did not influence the risk estimates. Further, the length of PPI exposure and actual PPI dose were not assessed. Prescription of less potent acid-reducing drugs such as H2-receptor antagonist was not included in the regression model as PPIs are more frequently prescribed within UK primary care settings. Other studies assessing the adverse events of these class of drugs have shown a stronger association with PPI, however, including them may have provided a proxy for a measure of a dose-response relationship [15–17]

6.6.3 Conclusion

There was a 2-fold risk in the onset of IBS following *Campylobacter* infection in patients with a PPI prescription, most notably in adult females below the age of 65. Future work needs to establish if a dose response-relationship exist.

Some patients with *Campylobacter* infection still received antibiotics for their infection on the same day as a diagnosis for infection, despite guidelines not to treat. This did not appear to be associated with the onset of sequelae following GI infection.

Chapter 7 will explore the healthcare resource usage patterns of patients with GI infection only and those who developed sequelae. This will provide further insights into how patient's characteristics may influence their healthcare resource usage and provide interesting avenues for future research on the influence of patient's age and socioeconomic status in the onset of sequelae.

6.7 References

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Chapter 7

The economic impact of sequelae of *Campylobacter* and non-typhoidal *Salmonella* infections amongst patients on the National Health Service in England, 2000-2015

7.1 Overview

This chapter describes the methods used to assess the impact of sequelae of *Campylobacter* and NTS infections healthcare resource use and the associated costs from the perspective of the payer, the National Health Service (NHS). It then continues by presenting and discussing the results of the analysis and implications for society. Further discussions on the main findings are presented in Chapter 8.

***Objective D**: To quantify the volume, type and costs of healthcare resources associated with sequelae of Campylobacter and NTS infections.*

7.2 Methods

7.2.1 Study population

A total of 17,108 patients were included in the health economic assessment. These were patients with relevant Read codes for the diagnosis of *Campylobacter* or NTS registered at up-to-standard CPRD practices with linkage to HES data between 1st January 2000 to 31st December 2015 to ensure full costing of all healthcare resource usage across both primary and secondary care settings. Patients form England without a linkage to HES (n = 2,729) were excluded. Eligible patients were registered with the practice for a minimum of 12 months before study entry (baseline) to ensure

adequate recording of baseline covariates. Censor date was defined as the earliest of the date of death, the patient's transfer out of practice date, or the practice's last collection date.

7.2.2 Data Sources

CPRD, as a data source for patient selection, primary care resource use, and its linkage capabilities to HES for all hospital admissions in England, was described extensively in Chapter 4. This section includes a description of other data sources for determining direct costs associated with healthcare resource utilisation and their applications in this thesis.

Primary healthcare utilisation (e.g. consultations) costs to the NHS are calculated nationally from unit costs (the cost of one unit of "output") and are reported along with social care costs by the Personal Social Services Research Unit (PSSRU), University of Kent [1]. These costs are updated annually to reflect the national provision of health and social care services and any associated policy changes. The PSSRU, 2014/15 was used to assign a unit cost to all consultations in primary care. Where a unit cost for a relevant service was not available (out-of-hours consultations), the most recent (2009/2010) published unit cost was used after adjusting it for inflation using the Hospital and Community Health Services pay and price inflation index (HCHS), a weighted average of two separate inflation indices, the pay cost index and the health service cost index [2].

The annual England Prescription Cost Analysis (PCA) publication of NHS Digital was the source for primary care medication costs [3]. The basic NHS net prices of the product by pack size are provided with the number of items, and the net ingredient cost of all prescriptions dispensed in the community and hospital prescriptions. They are grouped according to version 17 of the British National Formulary (BNF) [4].

Laboratory and diagnostic test costs were available from secondary care sources. All NHS secondary care providers in England are required to submit annual cost information about all activities such as diagnostic tests, operations, and procedures performed since 1998 to the DHSC

[5]. These secondary care costs are used to produce the unit costs to the payer, the NHS, in providing healthcare to its patients, and allow comparisons across hospital providers. They are calculated as weighted averages and published annually as the National Schedule of Reference Costs (hereby referred to as reference costs) [5]. The 2014/15 reference costs were used to assign a unit cost to all tests in primary care.

In England, hospital contacts are costed using a form of diagnosis-related group (DRG) payment mechanism known as healthcare resource groups (HRGs). Each HRG, like other DRGs in high-income countries, is a cluster of clinically meaningful ICD-10 and OPCS codes as recorded in HES that consume similar amounts of healthcare resources [6]. The assigned HRG attracts a reference cost or tariff price depending on the costing approach adopted. The tariff is a nationally set price for the reimbursement of hospitals through the payment by results system for the treatment of patients within an HRG group [7]. I chose reference costs as the unit costs for all HRGs to inform resource allocation for future economic models.

Researchers and practitioners can assign relevant HRG at provider level, FCE or spell level using a grouping software (grouper) based on a hierarchical algorithm generated by the National Casemix Office [8]. HRG4, the current version in use was implemented in the 2007/2008 financial year. It is updated annually to reflect changes in clinical practice and changes to policy that may have occurred over time [6]. To ensure changes in cost reflected changes in utilisation rather than changes within the HRG algorithm or reference costs, the same HRG grouping algorithm was used for all data in all years. I used the NHS Digital 2014/2015 grouper software as it was the most recent for the latest data available for patients in the cohort. For consistency, I used the 2014/2015 reference costs.

7.2.3 Primary care resource use and costs

Primary care resource use for each patient was extracted from CPRD. Healthcare resource use was stratified by the subcategory of interest: consultations, tests, and prescriptions per patient. Costs were computed by multiplying units of resource use by their unit costs (Appendix 7-1).

Consultations

All consultations, as recorded in the CPRD consultation file, up to five years before and after the index date for *Campylobacter* or NTS infections were considered. These were classified by consultation and staff type and included GP consultations in surgery, by telephone and at home/out-of-hours, and nurse consultations in surgery and at home/out-of-hours (Appendix 7-1) [9,10]. Associated unit costs were assigned as identified in the PSSRU 2014/2015 (Appendix 7-2) [1]. It was possible for a patient to consult on the same day with two different staff categories and through different modes, e.g. telephone consultation with a nurse and surgery consultation with a GP. These consultations were considered separately, and costs attached accordingly. Duplicate records with the same staff category and consultation type on the same date for the same patient were excluded. Records with unknown staff category were also excluded (0.7%).

Prescriptions

Each prescription for each patient recorded in the CPRD therapy file up to five years before and after the index date for *Campylobacter* or NTS infection was identified. Drugs were classified according to their BNF chapter, and the corresponding mean cost was attached according to the 2014 prices from the PCA [3]. Where missing data for the specific drug supplied prevented the use of this approach, the 2014 median prescription cost, as reported in the PCA, was attributed to the relevant drug. Costs were attached to PPI and the three classes of antibiotics (cephalosporins, quinolones and macrolides) from their specific BNF chapter subparagraph. These costs selected from the BNF chapter subparagraph were subtracted from the relevant BNF chapter to prevent double costing (Appendix 7-2).

Tests

All individual tests for each patient recorded in the CPRD test file, up to five years before and after the index date for *Campylobacter* or NTS infections, were identified. Tests were categorised as laboratory tests (clinical biochemistry; haematology; microbiology) and other diagnostic services (e.g. imaging), and the relevant unit costs were attached (Appendix 7-2). Some laboratory tests are performed in batches. These batches of tests were identified through the help of an academic GP and according to current practices (Appendix 7-3) [11]. For each patient, each batch of tests or any sub-group within the same batch recorded on the same day were counted as one test only.

Tests routinely performed by a GP during a regular consultation, such as weight measurement, blood pressure and other physical examination, were excluded to avoid double counting as these tests were already incorporated in the GP consultation costs (Appendix 7-3) [12,13].

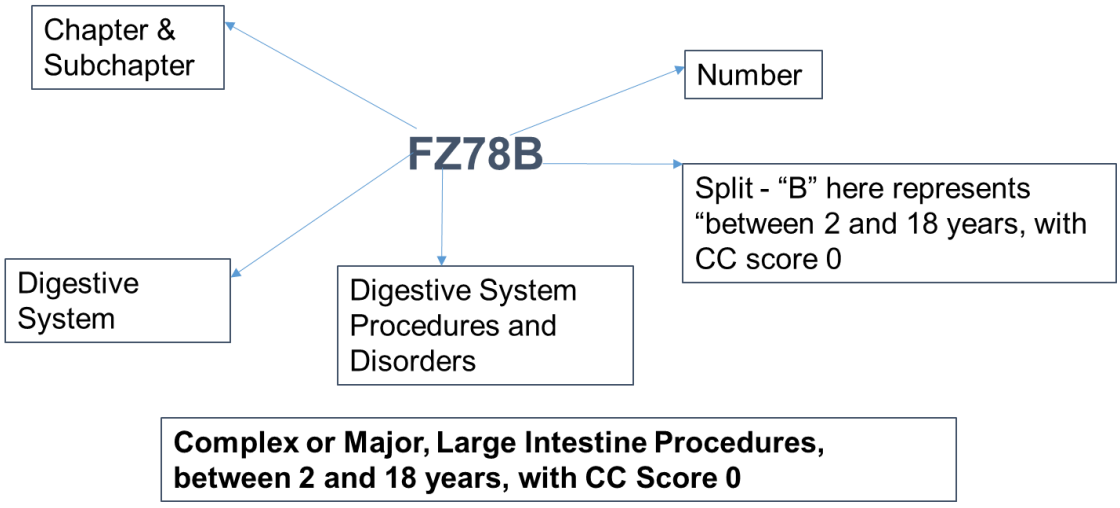
7.2.4 Secondary care

All admitted patient care (APC), and outpatient records in HES data in the five years before and after the index date of *Campylobacter* or NTS infections were extracted and analysed. Standard practices were followed to determine the HRG for each patient's hospital encounter.

For APC, the spell level record was used to determine the HRG. This required reformatting of the HES data. All episodes were grouped into spells, which include patient demographics, all diagnoses fields, all specialists seen within the spell period, all investigations, and procedures (excluding blood tests). The reformatted spell level records were parsed through the grouper to determine the HRG [8]. The main driver for deriving the HRG code is the dominant procedure. Procedures are ranked according to their hierarchy values. The procedure with the highest hierarchy value is classified as the dominant procedure. If a dominant procedure is not present, the primary diagnosis field is used. Once the dominant procedure is known, the grouper considers the presence or absence of complications and comorbidities (CC) as illustrated in Figure 7-1 [6,8].

The final cost of care for each spell was derived by linking the assigned HRG code to the relevant reference costs according to the nature of admission (elective vs emergency) and the excess length of stay where applicable. Some HRGs attract additional costs known as unbundled HRGs, which are components within a care pathway which are costed separately such as chemotherapy and diagnostic imaging; these costs were also considered [7] (Appendix 7-4).

Figure 7-1 The format of an HRG



Source: Adapted from NHS Digital - The science of casemix [8]

Outpatients' procedures were also reformatted for the same time window and processed into the relevant HRGs. The allocated HRGs were linked to the NHS 2014/2015 reference costs based on the treatment function code and the attendance type. The treatment function code represents the specialised service within which the patient is treated, and the attendance type in the reference cost is coded as first or follow-up visit. All attendances were considered as single consultant appointments for costing purposes and not multidisciplinary team appointments. Outpatients attendances with no procedures were not parsed through the grouper, but costs were assigned using the NHS 2014/2015 reference costs.

HRGs for colonoscopies were specifically identified from the APC and Outpatients data. Each procedure was classified as elective or non-elective according to the coding in the HES dataset. The NHS 2014/2015 reference costs were attached.

7.2.5 Statistical analysis

Average quarterly resource use and costs accrued by patients up to a year before and after index date of *Campylobacter* or NTS infection were computed, and all the available data for the two-year (8 quarters) period were considered. The average resource use and costs accrued by each patient in the quarters' pre- and post-infection for patients with either of the selected GI infection only were evaluated to assess the impact of the diagnosis of the selected GI infections on resource use and costs. The impact of sequelae on resource use/costs were assessed by comparing the average resource use/costs in the pre-and post-infection period for the patients with either of the selected GI infections who developed sequelae in comparison with patients with the selected GI infections only. Resource use and costs accrued on the index date of the selected GI infections were excluded to prevent inflating the average resource use/costs in the periods before infection.

The average annual resource use and costs were calculated to determine whether the pattern of resource use and costs varied systematically over time between the two groups of patients before and after the index date, and compared for both groups of patients in the five years before and after the index date in a secondary analysis. All the ten years were considered even if the data on healthcare utilisation and costs for some of the patients were available for less than ten years, provided that data were available on at least some of the patients within the study population. Therefore, average resource use and costs were calculated on a variable number of patients for each year over the ten years of follow-up.

Both quarterly and yearly analyses were stratified by resource use and cost category of interest, namely consultations, tests, prescriptions, outpatients, admissions, and colonoscopies. A total cost for each patient was calculated by summing up all individual category of cost.

The annual total cost impact of sequelae on the NHS in England was calculated by a three-step approach. The first step was to determine the **mean annual cost impact per patient**. This was estimated by multiplying the per patient mean quarterly difference in the total costs accrued by patients with the selected GI infection who developed sequelae in comparison with patients with the selected GI infection only by four. The second step was to determine the **expected number of people who will develop sequelae in England amongst those that consult their GP for the selected GI infections**. This was done by multiplying the number of people expected to consult their GP for *Campylobacter*/NTS infections, as obtained by published estimates from IID2 study [14], by the rate of sequelae amongst *Campylobacter*/NTS patients in the cohort (Chapter 5). The third and final step was to **estimate the total cost impact of sequelae in England** by multiplying the results from step 1 and step 2 (Box 1).

Chapter 7 - Box 1. The total cost impact of sequelae of *Campylobacter*/NTS infections on the NHS in England

Step 1: Determine mean annual cost impact per patient

Mean annual cost impact of sequelae per patient =

DID† per quarter X 4

Step 2: Determine expected number of people with sequelae annually

Expected number with sequelae =

Number of patients with selected GI infection who consulted their GP x rate of sequelae

Step 3: Determine mean total annual cost impact of sequelae on the NHS in England

Mean total annual cost impact of sequelae on NHS in England =

Mean annual cost impact of sequelae (from step 1) * Expected number with sequelae (step 2)

†DID - Difference in the mean total costs accrued by patients with the selected GI infection and sequelae in comparison to the mean total costs accrued by patients with the selected GI infection only.

Assumptions
Step 1 – Cost is based on annual incidence amongst those without previous history of the selected GI infections and does not capture those who may have had a prior GI infection before entry into the cohort.
Step 2 –It is assumed that i) rate of sequelae is the same among patients presenting to primary care and ii) patients who develop sequelae consult their GP

All cost categories were treated as continuous variables and reported as the number of events per patient per quarter/year. Resource use rates and mean costs, before and after the index date for the selected GI infections were reported together with their standard errors. Rates and mean differences in observed resource use and costs between the two periods (i.e. before and after the selected GI infections index date) were reported alongside 95% C.I. Total costs were further stratified by sex, age, the presence or absence of comorbidities using the CCI and SES using IMD quintiles. Statistical significance in mean estimates was evaluated using Student's two-sided t-test. Statistical significance was set at *P*-values less than 0.05.

7.3 Results

7.3.1 Baseline characteristics

The demographics of patients in the cohort have been previously described in Chapter 5. Briefly, patients with sequelae (n=286) were more likely to be female than patients with GI infection only (n =16,822) (63% vs 48%, $P<0.001$). There were no significant differences in patients' deprivation quintiles, smoking status, presence or absence of comorbidity amongst patients with GI infection only and those who developed subsequent sequelae (Table 7-1).

Table 7-1 Baseline characteristics of patients with *Campylobacter* or NTS infection with or without sequelae in England, 2000-2015

	Campylobacter			**NTS**		
	GI infection only (N = 14,638)	**GI with sequelae (N=229)**	***P*-value**	**GI only (N = 2,184)**	**GI with sequelae (N=57)**	***P*-value**
	N (%)	N (%)		N (%)	N (%)	
Age group						
Age, mean	44.9 (21.0)	46.0 (17.1)	0.41	37.0 (23.0)	42.7 (17.0)	0.064
Sex						
Male	7,720 (52.7)	89 (38.9)	<0.001	1,035 (47.4)	18 (31.6)	0.018
Female	6,918 (47.3)	140 (61.1)		1,149 (52.6)	39 (68.4)	
IMD						
1	4,366 (29.8)	74 (32.5)	0.33	607 (27.8)	17 (29.8)	0.65
2	3,824 (26.1)	68 (29.8)		511 (23.4)	16 (28.1)	
3	2,893 (19.8)	36 (15.8)		442 (20.3)	13 (22.8)	
4	2,212 (15.1)	34 (14.9)		373 (17.1)	7 (12.3)	
5	1,333 (9.1)	16 (7.0)		249 (11.4)	4 (7.0)	
Smoking status						
Never smoked	9,225 (63.0)	138 (60.3)	0.096	1,470 (67.3)	37 (64.9)	0.92
Ever smoked	4,413 (30.1)	67 (29.3)		600 (27.5)	17 (29.8)	
Missing	1,000 (6.8)	24 (10.5)		114 (5.2)	3 (5.3)	
CCI_presence or absence						
No comorbidity	9,559 (65.3)	142 (62.0)	0.3	1,591 (72.9)	41 (71.9)	0.88
1 or more CCI	5,079 (34.7)	87 (38.0)		593 (27.2)	16 (28.1)	

7.3.2 Healthcare resource utilisation

Over 50% of all healthcare resource use amongst all patients in the cohort regardless of sequelae status, were prescriptions. Outpatients, inpatient admissions, and colonoscopy accounted for less than one per cent of the overall resource use (Table 7-2a and Table 7-2b).

Table 7-2a Average quarterly healthcare utilisation amongst patients with *Campylobacter i*nfection (with or without sequelae) in the quarters preceding and after infection in England, 2000-2015

	GI only			GI with sequelae			Impact of sequelae		
Category	**After (A)** [1]	**Before (B)** [1]	**Difference (A-B)** [2]	**After (A)** [1]	**Before (B)** [1]	**Difference (A-B)** [2]	**After[3]**	**Before[4]**	**DID**
Consultations	1.9 (0.0167)	2.1 (0.0163)	-0.3 (-0.3 -0.2)*	3.3 (0.184)	2.8 (0.127)	0.5 (0.04, 1.0)*	1.4 (1.2, 1.7)**	0.7 (0.4, 0.9)**	0.8 (0.6, 1.0)**
Prescriptions	5.3 (0.079)	5.4 (0.075)	-0.06 (-0.3, 0.2)	7.3 (0.567)	6.1 (0.521)	1.2 (-0.3, 2.7)	2.0 (0.8, 3.3)*	0.73 (-0.5, 1.9)	1.3 (0.8, 1.8)**
Tests	1.6 (0.023)	1.9 (0.023)	-0.3 (-0.4, -0.2)*	3.6 (0.283)	2.5 (0.219)	1.1 (0.4, 1.8)*	2.0 (1.6, 2.4)*	0.6 (0.3, 1.0)**	1.4 (1.1, 1.7)**
Outpatients	0.04 (0.0020)	0.04 (0.00160)	0.006 (0.001, 0.01)*	0.09 (0.0232)	0.08 (0.0243)	0.01 (-0.06, 0.08)	0.05 (0.0, 0.1)*	0.05 (0.02, 0.1)**	0.004 (-0.03, 0.04)
Admissions	0.10 (0.00239)	0.09 (0.00268)	0.0003 (-0.007, 0.007)	0.3 (0.0636)	0.01 (0.0154)	0.2 (0.03, 0.3)*	0.17 (0.1, 0.2)**	0.007 (-0.03, 0.1)	0.2 (0.1, 0.2)**
Colonoscopy	0.003 (0.00238)	0.002 (0.000201)	0.0009 (0.0003, 0.002)*	0.02 (0.00488)	0.003 (0.00188)	0.02 (0.01, 0.03)*	0.02 (0.02, 0.02)**	0.0009 (-0.002, 0.004)	0.003 (0.02, 0.03)**
Total	**8.9 (0.104)**	**9.5 (0.010)**	**-0.6 (-0.9, -0.3)***	**14.6 (0.876)**	**11.6 (0.794)**	**3.1 (0.7, 5.4)***	**5.7 (4.0, 7.3)****	**2.1 (0.5, 3.6)***	**3.6 (2.8-4.4)****

[1] Standard error in parentheses; [2] Confidence interval in parentheses; After[3](Mean resource use quarters after for patients with selected GI and sequelae – Mean resource use quarters after for patients with selected GI infection only) Before[4]-(Mean resource use quarters before for patients with selected GI and sequelae – Mean resource use quarters before for patients with selected GI infection only); DID – Difference in mean differences (After[3] – Before[4]); *Independent Student's t-test *P*-value <0.05; **Independent Student's t-test *P*-value <0.001

Table 7-2b Average quarterly healthcare utilisation amongst patients with NTS infection (with or without sequelae) in the quarters preceding and after infection in England, 2000-2015

	GI only			GI with sequelae			Impact of sequelae		
Category	**After (A)** [1]	**Before (B)** [1]	**Difference (A-B)** [2]	**After (A)** [1]	**Before (B)** [1]	**Difference (A-B)** [2]	**After**[3]	**Before**[4]	**DID**
Consultations	2.0 (0.039)	1.8 (0.043)	-0.2 (-0.3, -0.03)*	3.4 (0.347)	2.5 (0.244)	0.9 (0.1, 1.8)*	1.6 (1.1, 2.2)**	0.5 (0.03, 1.0)*	1.1 (0.7, 1.5)**
Prescriptions	4.0 (0.167)	4 .1(0.174)	0.1 (-0.6, 0.4)	6.7 (1.321)	4.8 (0.866)	1.9 (-1.2, 5.0)	2.7 (0.6, 4.8)*	0.7 (-1.4, 2.9)	2.0 (0.8, 3.2)*
Tests	1.4 (0.049)	1.4 (0.046)	-0.02 (-0.2, 0.1)	2.9 (0.489)	1.8 (0.263)	1.1 (0.004, 2.2)	1.5 (0.9, 2.1)**	0.4 (-0.2, 0.9)	1.1 (0.6, 1.7)**
Outpatients	0.03 (0.0053)	0.021 (0.0027)	0.005 (-0.006, 0.02)	0.07 (0.029)	0.1 (0.0275)	0.004 (-0.08, 0.08)	0.04 (-0.02, 0.1)	0.04 (0.007, 0.07)*	-0.001 (-0.06, 0.06)
Admissions	0.1 (0.019)	0.11 (0.019)	-0.1 (-0.06, 0.04)	0.2 (0.0349)	0.1 (0.0269)	0.08 (-0.004, 0.2)	0.07 (-0.2, 0.3)	-0.2(-0.3, 0.2)	0.09 (0.02, 0.2)*
Colonoscopy	0.003 (0.000546)	0.0016 (0.000457)	0.001 (-0.0004, 0.002)	0.02 (0.00853)	0.004 (0.00439)	0.01 (-0.006, 0.03)	0.01 (0.008, 0.02)**	-0.003(-0.003, 0.009)	0.01 (0.003, 0.02)*
Total	**7.4(0.229)**	**7.6(0.227)**	**-0.3 (-0.9, 0.4)**	**13.3 (1.889)**	**9.2 (1.216)**	**4.0(-0.4, 8.5)**	**5.9 (3.1, 8.7)****	**1.6(-1.2, 4.4)**	**4.3 (2.7, 5.9)****

[1] Standard error in parentheses; [2] Confidence interval in parentheses; After[3](Mean cost quarters after for patients with selected GI and sequelae – Mean cost quarters after for patients with selected GI infection only) Before[4]-(Mean cost quarters before for patients with selected GI and sequelae – Mean cost quarters before for patients with selected GI infection only); DID – Difference in mean differences (After[3] – Before[4]); *Independent Student's t-test *P*-value <0.05; **Independent Student's t-test *P*-value <0.001

Amongst patients with the selected GI infection only, the average resource use per patients with *Campylobacter* infection in the quarters post-infection was significantly lower for consultations (-0.3, 95% C.I (0.3, -0.2), *P*<0.001), and tests (-0.3, 95% C.I (-0.4, -0.2), *P*<0.001) with a marginally higher rate of outpatient appointments (0.006, 95% C.I (0.001, 0.01), *P*=0.013), and colonoscopy (0.0009, 95% CI (0.0003, 0.002), *P*=0.003) compared with the average resource use per patient in the quarters pre-infection (Table 7-2a). For NTS patients, the quarterly average resource use per patient pre- and post-infection were similar across all domains of healthcare except for a marginally lower rate of consultations in the quarters post-infection (-0.2, 95% C.I -0.26, -0.03, *P*=0.012) (Table 7-2b).

When subcategories within each healthcare resource type were considered for all patients regardless of their sequelae status (both *Campylobacter* and NTS patients, considered together due to small numbers of patients with sequelae), face-to-face (surgery) GP consultations and clinical biochemistry were the most common events for their respective domains. For prescriptions, excluding the other category, prescriptions for the cardiovascular system (BNF-chapter 2) was the most frequent for patients with the selected GI infection only; while for patients with the selected GI infection and sequelae, prescriptions for the central nervous system (BNF-chapter 4) was the most frequent (Figure 7-3).

In relation to hospital admissions, patients with the selected GI infections only had a significantly longer length of stay in the quarter's pre-infection (mean difference, -0.09 days, 95% C.I (-0.10, -0.08), *P*<0.001) in comparison with patients with the selected GI infections and sequelae (mean difference, 0.09 days, 95% C.I (-0.11, 0.29), *P* =0.376). "Digestive system Procedures and Disorders" (code FZ) was the most frequent HRG subchapter for all patients both in the quarters pre-infection (selected GI infections only, 19.2% vs selected GI infections with sequelae, 38%) and after (selected GI infections only, 17.8% vs. selected GI infections with sequelae, 65%).

Figure 7-3 Quarterly resource use by subcategories of resource type amongst *Campylobacter* and NTS patients with GI infection only and those who developed subsequent sequelae in England, 2000-2015

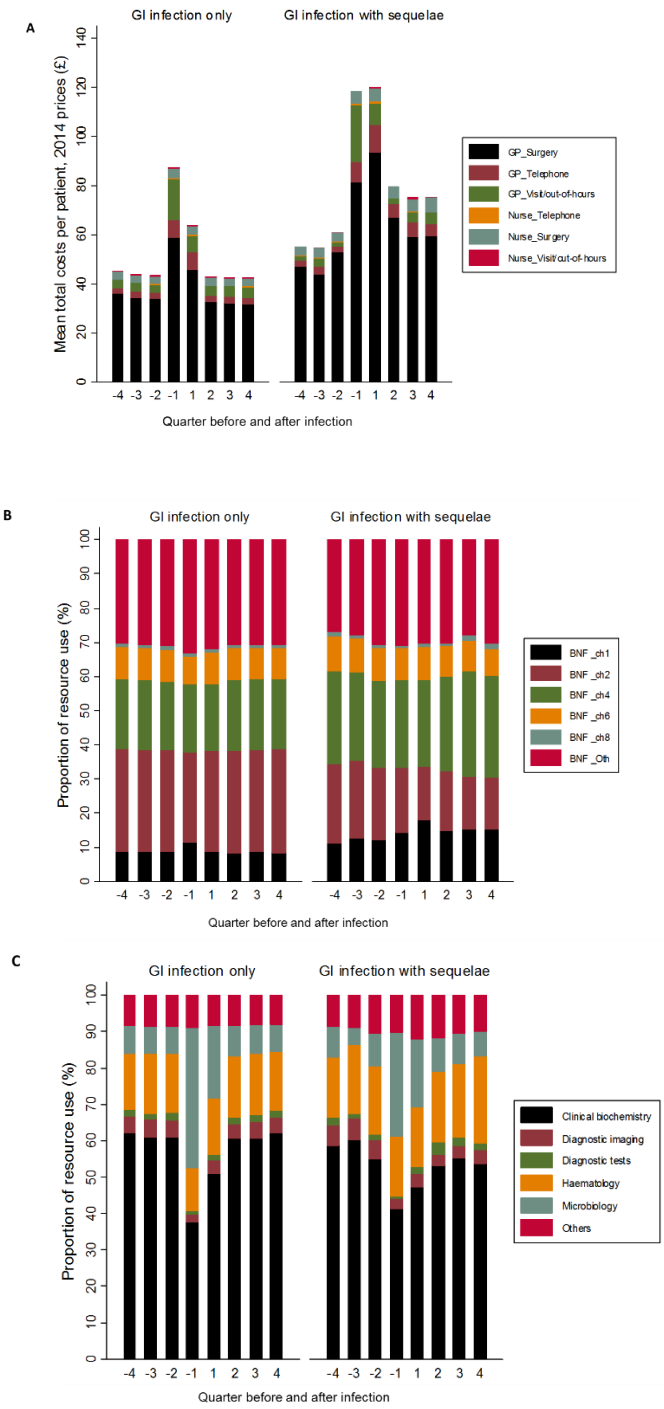


Figure 7-3 shows primary healthcare resource domains stratified by their subcategories; A- Consultations, B – Prescriptions, and C – Tests

Impact of sequelae on resource use following gastrointestinal infections

Amongst *Campylobacter* patients, there was a significant impact of sequelae on overall healthcare resource utilisation (3.6, 95% C.I (2.8, 4.4), $P<0.001$), and on each individual domain except for outpatients (0.004, 95% C.I (-0.03, 0.04), $P=0.828$) when differences in the pre- and post-infection periods amongst patients with the selected GI infection only and those who developed sequelae were considered. This was as a result of significantly higher rates of total healthcare utilisation both in the quarters pre-infection (2.1, 95% C.I (0.5, 3.6), $P=0.011$), and post-infection (5.7, 95% C.I (4.0, 7.3), $P<0.001$) amongst *Campylobacter* patients with sequelae in comparison to their GI infection only counterparts (Table 7-2a). Elevated rates of healthcare utilisation in the quarters pre-infection were due to consultations (0.7, 95% CI (0.4, 0.9), $P<0.001$), tests (0.6, 95% C.I (0.3, 1.0), $P<0.001$), and outpatient attendances (0.05, 95% C.I (0.02, 0.1), $P<0.001$). For the quarters post-infection, the increase in utilisation was observed across all domains of healthcare. However, consultations (1.4, 95% C.I (1.2, 1.7), $P < 0.001$), tests (2.0, 95% C.I (1.62, 2.36), $P<0.001$), and prescriptions (2.0, 95% C.I (0.8, 3.3), $P=0.001$) were the major drivers (Table 7-2a).

For NTS patients, there was also a significant impact of sequelae on overall healthcare resource utilisation (4.3, 95% C.I (2.7, 5.9), $P<0.001$), and on each individual domain, except for outpatient attendances (0.04 95% CI (-0.02, 0.10), $P=0.226$), and hospital admissions (0.1, 95% CI (-0.2, 0.3), $P = 0.56$) when differences in the pre- and post-infection periods amongst patients with GI infection only and those who developed sequelae were considered (Table 7-2b). This was as a result of significantly higher total healthcare utilisation in the quarters post-infection for patients with sequelae in comparison with their GI infection only counterparts (5.9, 95% CI (3.1, 8.7), $P<0.001$). (Table 7-2b).

Temporal analysis of resource utilisation

Further considerations of when resource use is greatest was considered for each of the four quarters pre- and post-infection for each healthcare resource domain (Figure 7-4). The period of greatest resource utilisation was in the immediate quarter pre-infection (-Q1) amongst patients with the selected GI infections only, while amongst patients with subsequent sequelae, the peak in resource use was in the immediate quarter post-infection (Q1). For patients with sequelae, the increased rate in Q1 was sustained at levels above baseline (-Q4) in the subsequent quarters despite an overall decline in resource use, except for prescriptions where levels continued to increase (Figure 7-4). Shorter periods (weeks) were considered in a post-hoc analysis for consultations and tests only (Appendix 7-5). For consultations, patients with the selected GI infection only had more events occurring in the first week (week 1) post-infection, while patients with additional sequelae presented peaks later in weeks 2-4 post-infection (Appendix 7-5). For tests, week one before infection was the primary driver of the elevated peaks registered in –Q1, in both patients with the selected GI infections and those with sequelae.

Figure 7-4a Average quarterly consultations, prescriptions and tests per patient amongst *Campylobacter* and NTS patients with or without sequelae in the quarters before and after infection

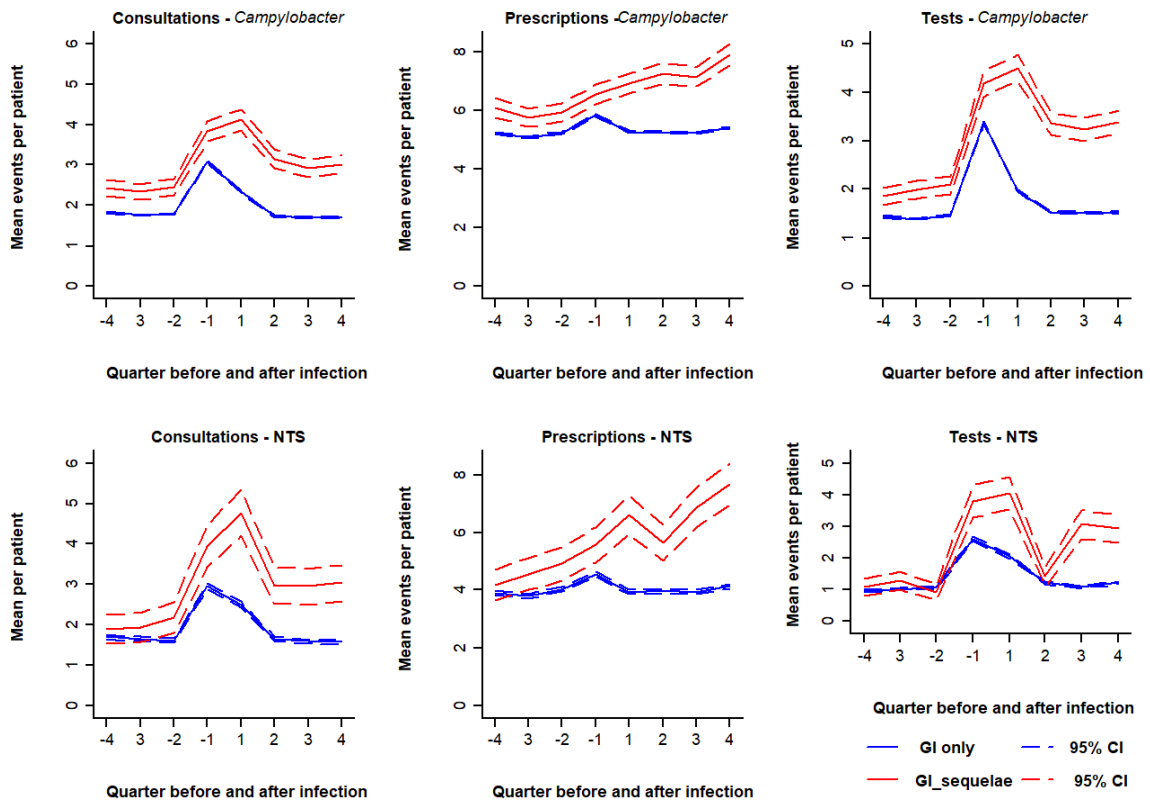


Figure 7-4a shows the mean number of events per patient. Different scales used for each type of event

Figure 7-4b Average quarterly outpatient attendances, hospital admissions and colonoscopies per patient amongst *Campylobacter* and NTS patients with or without sequelae in the quarters preceding and after infection

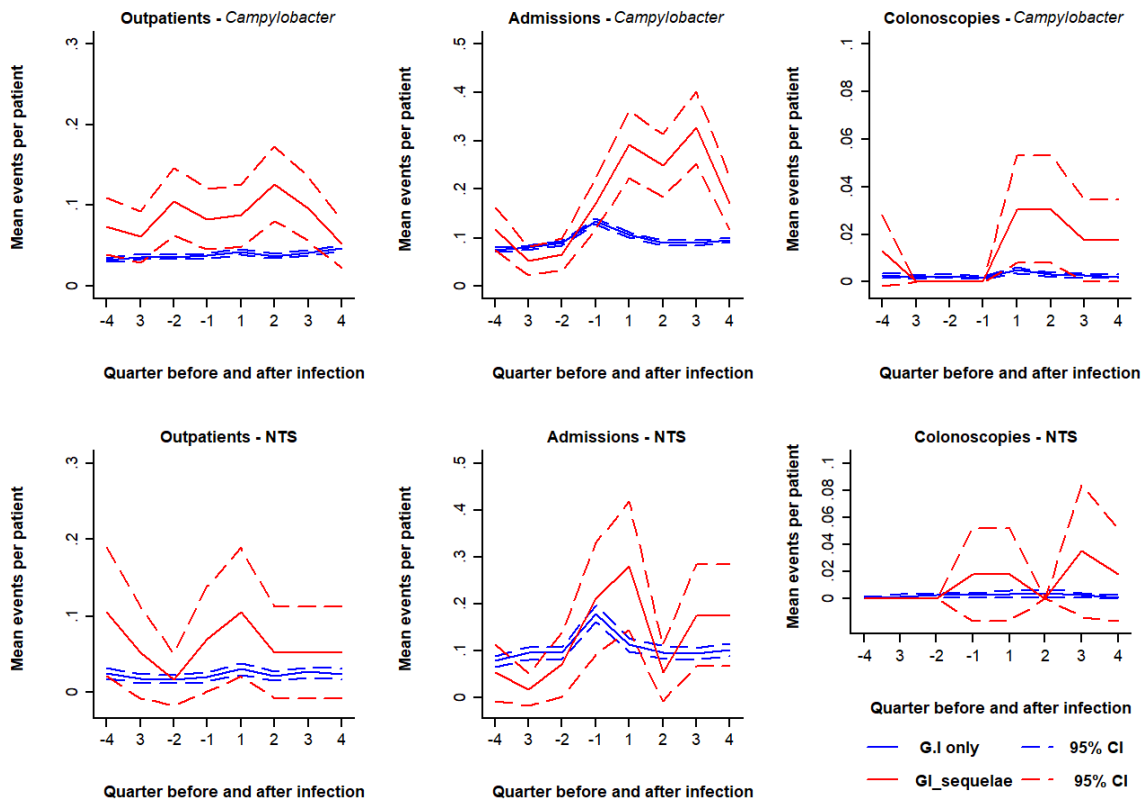


Figure 7-4b shows the mean number of events per patient. Different scales used for each type of event

7.3.3 Costs associated with gastrointestinal infection with or without sequelae

Total average quarterly cost per patient was approximately 10% lower post-infection than costs accrued pre-infection amongst patients with GI infection only. The reduction in costs post-infection (*Campylobacter*, -£19.4, 95% C.I (-£30.4, -£8.4), $P<0.001$; NTS, -£26.5, 95% C.I (-£56.1, £3.6), $P=0.085$) was due to decreased consultations and hospital admissions costs, although the cost differences were not all statistically significant for both *Campylobacter* and NTS patients (Table 7-3a and Table 7-3b).

Amongst patients with sequelae, the opposite was observed with significantly higher costs (50%) post-infection (*Campylobacter*, £311.6, 95% C.I (£127.3, £495.9), *P*<0.001; NTS, £185.3, 95% C.I (£30.4, £340.2) *P*=0.001), mainly driven by hospital admissions accounting for over half of the total costs (*Campylobacter* patients, 65%, £380.5/£586.7; NTS patients 52%, £198.1/£385.7) (Table 7-4a and Table 7-4b). Although other healthcare resource domains contributed to the increased costs in the quarters post-infection for sequelae patients, the cost differences were only statistically significant for hospital admissions (£265.8, 95% C.I (£93.8, £437.7), *P* =0.003), and colonoscopy (£11.0, 95% CI (£5.6, £16.4), *P* < 0.001) amongst *Campylobacter* patients; while for NTS patients, hospital admissions (£62.2, 95% CI(£6.4, £252.8) *P* =0.04), and tests (£9.7, 95% CI (£0.7, £18.7) *P* =0.004) were statistically significant (Table 7-3a and Table 7-3b).

Impact of sequelae on costs following gastrointestinal infections

Costs in the quarters post-infection were significantly higher for both *Campylobacter* (£331.0, 95% C.I (260.7, £401.37) *P*<0.001), and NTS (£211.0, 95% C.I (£58.8, £364.3) *P*<0.001) patients with sequelae in comparison to patients with these selected GI infections only (Table 7-3a and Table 7-3b). The £120 mean difference in cost amongst *Campylobacter* and NTS patients was not significant due to the wide confidence intervals for both groups of patients.

The impact of sequelae on costs accrued amongst *Campylobacter* patients were observed across all domains of healthcare resource, driven by hospital admissions (£275.5, 95% CI (£208.5, £342.4), *P*<0.001). For NTS patients with sequelae, significant impact on cost was observed on all healthcare resource domains except for outpatient attendances (-£1.2, 95% C.I (-£12.3, £9.5), *P* = 0.837).

Total costs implications for the NHS

Amongst patients with *Campylobacter* who developed sequelae, additional annual costs imposed by sequelae to the NHS is approximately £1,324 per case, which is equivalent to an annual estimated cost of £1,254,723.0, 95% CI (£881,561.0, £1,785,827.0) for all patients who may have consulted

their GP for their infection in England. Correspondingly for NTS infections, ~£884 in additional costs is incurred by the NHS leading to a total cost of £223,580.0, 95% CI (£92,058.0, £542,920.0) annually (Appendix 7-6 for calculation using steps in Box 1 on page 159).

Table 7-3a Average quarterly healthcare costs amongst patients with *Campylobacter* infection with or without sequelae in quarters preceding and after infection, 2000-2015

	GI only			GI with sequelae			Impact of sequelae		
Category	**After (A)** [1]	**Before (B)** [1]	**Difference (A-B)** [2]	**After (A)** [1]	**Before (B)** [1]	**Difference (A-B)** [2]	**After**[3]	**Before**[4]	**DID**[5]
Consultations	£47.8(0.476)	£56.4 (0.468)	£-8.6 (-£10.0, -£7.3)*	£85.4 (4.785)	£74.5 (4.493)	-£10.8 (-£2.1, £23.7)	£37.6 (£30.1, £45.2)**	£18.2 (£10.7, £25.6)**	£19.5 (£13.4, £25.6)**
Prescriptions	£44.0 (0.691)	£44.5(0.481)	-£0.5 (-£2.4, £1.4)	£68.6 (5.668)	£53.9 (5.122)	£14.7 (-£0.3, £29.7)	£24.6 (£13.7, £35.6)**	£9.4 (-£1.1, £19.9)	£14.7 (£13.9, £15.6)**
Tests	£12.5 (0.156)	£10.7 (0.168)	-£1.8 (-£2.3, -£1.4)*	£22.7 (2.145)	£18.1 (1.596)	£4.6 (-£0.7, £9.8)	£12.0 (£9.3, £14.6)**	£5.6 (£3.1, £8.06)**	£6.4 (£3.6, £9.3)**
Outpatients	£3.8 (0.253)	£3.04 (0.204)	£0.7 (£0.1, £1.4)*	£17.01 (8.429)	£12.3 (6.588)	£4.76 (-£16.3, £25.8)	£13.2 (£8.8, £17.7)**	£9.2 (£5.6, £12.8)**	£4.0 (-£0.3, £8.4)
Admissions	£105.7 (3.49)	£115.4 (3.424)	-£9.7 (-£19.3, -£0.1)	£380.5 (83.958)	£114.7 (24.668)	£265.8 (£93.8, £437.7)*	£274.8 (£216.4, £333.3)**	-£0.6 (-£54.6, £53.4)	£275.5 (£208.5, £342.4)**
Colonoscopy	£1.7 (0.124)	£1.2 (0.102)	£0.5 (£0.2, £0.8)*	£12.6 (2.574)	£1.6 (0.924)	£10.97 (£5.6, £16.4)*	£10.9 (£8.8, £12.9)**	£0.4 (-£1.2, £2.0)	£10.4 (£7.4, £13.0)**
Total	**£213.6 (4.023)**	**£233.0 (2.815)**	**-£19.4 (-£30.4, -£8.4)***	**£586.7 (88.484)**	**£275.1 (31.142)**	**£311.6 (£127.3, £495.9)***	**£373.2 (£304.5, £439.8)****	**£42.1 (-£20.0, £104.3)**	**£331.0 (£260.7, £401.4)****

[1] Standard error in parentheses; [2] Confidence interval in parentheses; After[3](Mean cost quarters after for patients with the selected GI infection and sequelae – Mean cost quarters after for patients with the selected GI infection only) Before[4]-(Mean cost quarters before for patients with the selected GI infection and sequelae – Mean cost quarters before for patients with the selected GI infection only); DID – Difference in mean differences (After[3] – Before[4]); *Independent Student's t-test *P*-value <0.05; **Independent Student's t-test *P*-value <0.001

Table 7-3b Average quarterly healthcare costs amongst patients with NTS infection with or without sequelae in quarters preceding and after infection, 2000-2015

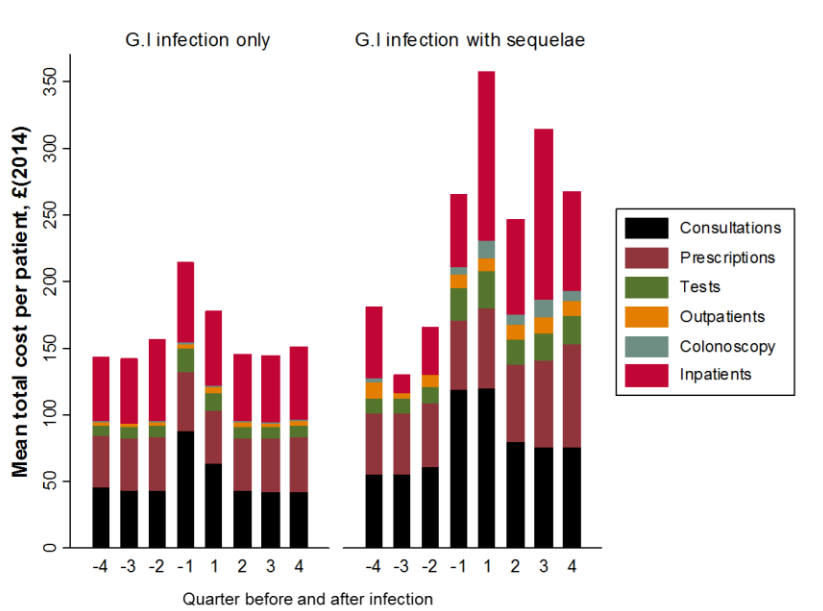
	GI only			GI with sequelae			Impact of sequelae		
Category	**After (A)[1]**	**Before (B)[1]**	**Difference (A-B)[2]**	**After (A)[1]**	**Before (B)[1]**	**Difference (A-B)[2]**	**After[3]**	**Before[4]**	**DID**
Consultations	£48.1 (1.186)	£53.6 (1.113)	-£5.5 (-£8.7, -£2.3)**	£89.6 (9.222)	£70.2 (7.587)	£19.4 (-£4.2, £43.1)	£41.5 (£26.9, £56.2)**	£16.6 (£2.9, £30.3)*	£25.0 (£12.4, £37.5)**
Prescriptions	£35.3 (1.541)	£35.8 (1.528)	-£0.5 (-£4.8, £3.7)	£63.0 (9.718)	£42.3 (7.839)	£20.8 (-£8.8, £50.4)	£27.8 (£8.7, £46.9)*	£6.50 (-£12.2, £25.2)	£20.8 (£18.5, £23.2)**
Tests	£9.7 (0.368)	£10.1 (0.384)	-£0.4 (-£1.5, £0.6)	£20.9 (4.035)	£11.2 (2.130)	£9.7 (£0.7, £18.7)*	£11.2 (£6.6, £15.9)**	£1.1 (-£3.6, £5.9)	£10.1 (£4.8, £15.4)*
Outpatients	£2.6 (1.029)	£1.7 (0.244)	£0.9 (-£1.2, -£3.0)	£5.3 (2.190)	£5.5 (2.473)	-£0.24 (-£6.8, £6.3)	£2.7 (-£9.9, £15.2)	£3.8 (£0.8, £6.9)*	-£1.2 (-£12.3, £9.5)
Admissions	£101.6 (10.076)	£122.9 (9.333)	-£21.3 (-£48.2, £5.7)	£198.1 (56.867)	£68.6 (25.165)	£62.2 (£6.4, £252.8)*	£96.5 (-£27.1, £220.2)	-£54.3 (-£167.9, £59.3)	£150. 8 (£2.4, £299.3)
Colonoscopy	£1.3 (0.280)	£0.8 (0.227)	£0.5 (-£0.2, £1.2)	£8.7 (4.248)	£2.6 (2.632)	£6.1 (-£3.8, £16.0)	£7.4 (£3.7, £11.0)**	£1.8 (-£1.1, £4.7)	£5.5 (£0.9, £10.2)*
Total	**£198.6 (11.165)**	**£224.9 (10.356)**	**-£26.5 (-£56.1, £3.6)**	**£385.7 (69.935)**	**£200.4 (34.967)**	**£185.3 (£30.4, £340.2)***	**£187.1 (£49.8, £324.4)***	**-£24.5 (-£150.7, £101.8)**	**£211.5 (£58.8, £364.3)***

[1] Standard error in parentheses; [2] Confidence interval in parentheses; After[3](Mean cost quarters after for patients with the selected GI infection and sequelae – Mean cost quarters after for patients with the selected GI infection only) Before[4]-(Mean cost quarters before for patients with the selected GI infection and sequelae – Mean cost quarters before for patients with the selected GI infection only); DID – Difference in mean differences (After[3] – Before[4]); *Independent Student's t-test *P*-value <0.05; **Independent Student's t-test *P*-value <0.001

Temporal analysis of costs

Total average costs per patient per quarter was significantly higher amongst patients with sequelae in –Q1 (mean difference and up to Q4) in comparison with patients with the selected GI infections only. Consultations and hospital admissions were the major drivers of costs in these periods. For patients with the selected GI infection only, the costs of consultations and hospital admissions also elevated the total average costs per patient for –Q1. (Figure 7-5).

Figure 7-5 Quarterly total costs per patient stratified by healthcare resource domain amongst patients with Campylobacter and NTS infections with GI infection only and those who developed sequelae



Cost of consultations doubled between -Q2 and -Q1 before infection for all patients (£41.5 to £86.0 for NTS GI infection only, £60.2 to £121.2 NTS GI infection with sequelae, £45.3 to £89.2, for *Campylobacter* with GI infection, and £62.3 to £115.3, for *Campylobacter* with GI infection and sequelae), and remained elevated until Q2 after infection, returning to baseline for patients with GI infection (Figure 7-6). Face-to-face (surgery) consultations with GP accounted for over 70% of all costs across all quarters for all patients regardless of sequelae status, except for -Q1, where

costs for visit/out-of-hours with a GP were up to 10 times that of -Q2 (GI infection only, £3.7 to £23.5, GI infection and sequelae £1.5 to £16.5) (Figure 7-7).

Figure 7-6a Average quarterly primary care contacts per patient amongst *Campylobacter* and NTS patients with or without sequelae in the quarters' pre- and post- infection

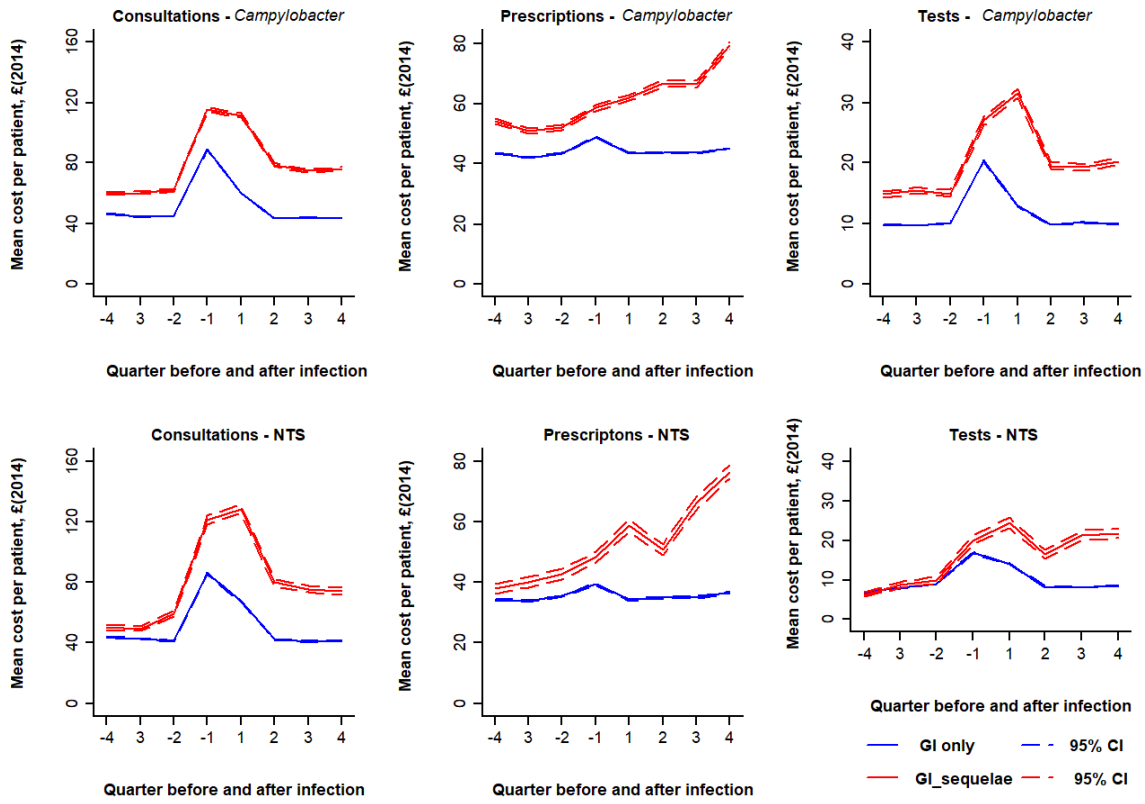


Figure 7-6a shows the average cost of primary care category per patient per quarter. Different scales used for each cost category.

Figure 7-6b Average outpatient, hospital admission, and colonoscopy costs per patient per quarter amongst *Campylobacter* and NTS patients with or without sequelae in the quarters' pre- and post- infection

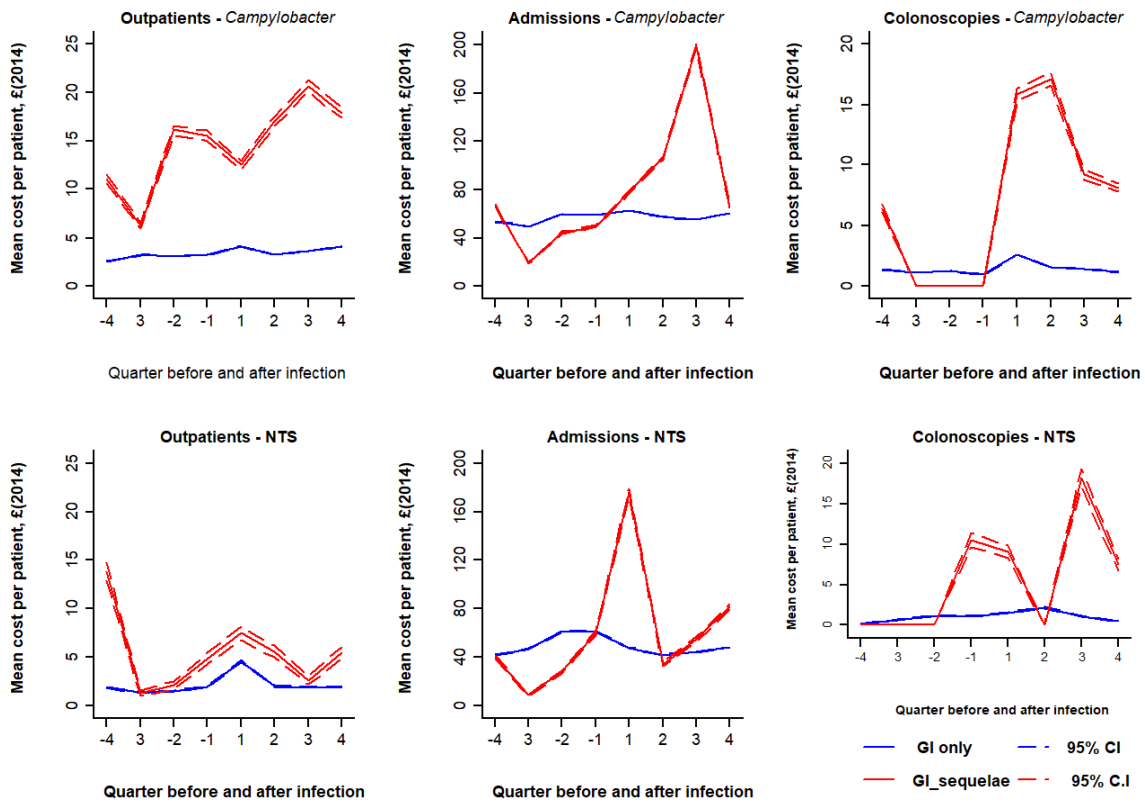


Figure 7-6b shows the average cost of secondary care category per patient per quarter. Different scales used for each cost category.

Costs of tests for all patients regardless of sequelae status followed a similar pattern of rising and falling in the periods' pre- and post-infection (Figure 7-6). In -Q3 and -Q4, over 60% of tests costs were as a result of diagnostic imaging. By -Q1 pre-diagnosis, diagnostic imaging costs had halved (GI infection only 30%, £11.3/£37.2; GI infection and sequelae, 35%, £16.5/£47.0), accounting for only approximately a third of all costs due to an increase instead in microbiology tests (£1.5 to £16.6 and £2.3 to £16.9 for patients with GI infection and those who develop sequelae respectively) (Figure 7-7).

Figure 7-7 Cost distribution by subcategories of consultations, tests and prescription amongst patients with *Campylobacter* and NTS infections only and subsequent sequelae

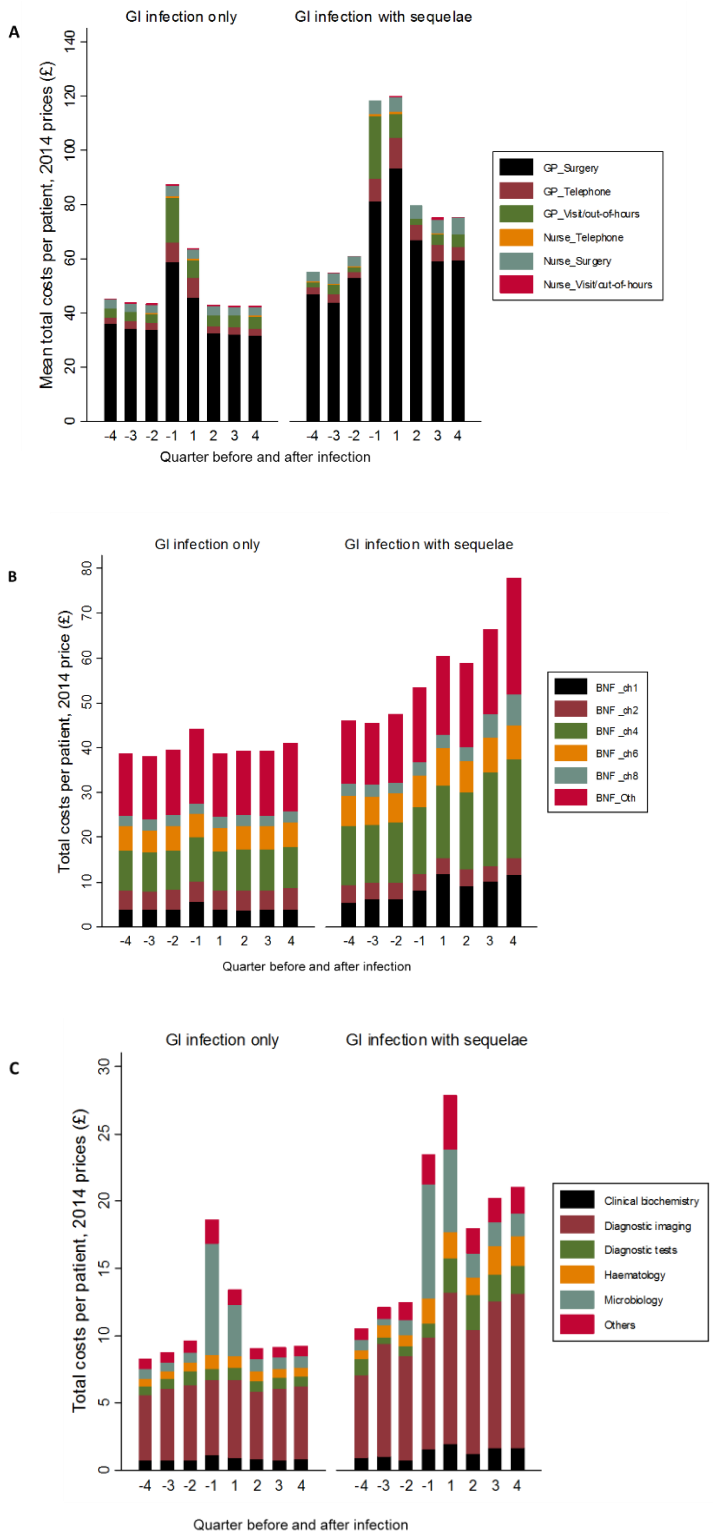


Figure 7-7 shows primary healthcare resource domains stratified by their cost subcategories; A- Consultations, B – Prescriptions, and C - Tests

Patient stratification and the impact of sequelae on healthcare costs

Total costs were stratified further by patients' sex, age, SES using IMD, and CCI (Table 7-3). Costs were significantly higher for males with selected GI infection and sequelae in the quarters post-infection (£472, 95% C.I (£153, £790.3) P =0.004) than females. Consequently, the impact of sequelae was more pronounced in males (£510.2, 95% C.I (£413.0, £607.3), P <0.001) than females (£183.9, 95% CI (£98.1, £269.7), P<0.001) when mean total cost differences between patients with the selected GI infections only and those with sequelae are compared for the periods pre-and post-infection

Amongst patients with the selected GI infections only, those aged 65 years and above accrued the highest total costs while those aged 0-18 years accrued the least costs both pre- and post-infection periods. Patients who subsequently developed sequelae had a similar pattern of cost distribution by age (Table 7-4). However, on comparison of patients with sequelae to their GI infection only counterparts, the impact of sequelae and patient's age on total costs was more pronounced in patients aged 65 years and above, £603.4, 95% CI (£130.6, £859.4), P<0.001) (Table 7-4).

Patients with the selected GI infections only living in the most affluent areas (IMD-1) accrued lower total costs in comparison with those living in the most deprived areas (IMD-5) in the quarters after infection (Table 7-4). For patients who subsequently developed sequelae, there was no clear distinction in the costs accrued by patient's SES as both patients in relatively affluent areas (IMD-2) and those in the most deprived areas (IMD-5) accrued the most costs in the quarters post-infection, although overall numbers of patients in each IMD-level were small (84 and 20 respectively). Consequently, the impact of sequelae was significant in these patients in comparison with patients living in any other IMD quintile with the GI infections only (IMD-2, £443.7, 95% C.I (£327.2, £560.2), P <0.001; IMD-5, £614.0, 95% C.I (£287.6, £940.3), P <0.001) (Table 7-4).

The presence of a comorbidity amongst patients with sequelae had a significant impact on costs accrued by these patients in the quarters post-infection in comparison with patients with the

selected GI infections only (£629.9, 95% CI (£495.2, £764.5), P <0.001), with a significant impact overall between this time period and the pre-infection period (£566.2, 95% CI (£418.6, £713.9), P <0.001) (Table 7-4).

Table 7-4 Total costs per patient by sex, age group and deprivation quintiles for patients with *Campylobacter* and NTS GI infections with or without sequelae in England, 2000-2015

	Patients with GI only (N= 16,822)				Patients with GI and sequelae (N = 286)				Impact of sequelae		
Stratum		**After**	**Before (B)**	**Difference (A-B)**	**Stratum**	**After**	**Before**	**Difference (A-B)**	**After[1]**	**Before[2]**	**DID[3]**
Males (n = 8,755)	Mean	£202.1	£253.3	-£51.2**	***Males (n = 107)***	£710.4	£238.4	£472.0*	£481.0**	-£29.2	£510.2**
	SE	4.976	4.920	6.998		156.340	40.459	161.491	47.429	43.499	49.554
	lcl	£192.4	£243.7	-£64.9		£400.4	£158.2	£153.6	£388.0	-£114.5	£413.0
	ucl	£211.9	£263.0	-£37.5		£1,020.3	£318.6	£790.3	£573.9	£56.1	£607.3
Females (n =8,067)	Mean	£254.0	£301.9	-£47.9**	***Females (n =179)***	£497.2	£363.7	£133.5	£235.4**	£51.5	£183.9**
	SE	5.860	5.757	8.215		68.959	34.344	77.038	40.500	38.171	43.776
	lcl	£242.5	£290.6	-£64.0		£361.12	£295.9	-£18.0	£156.0	-£23.3	£98.1
	ucl	£265.5	£313.2	-£31.8		£633.28	£431.5	£285.0	£314.8	£126.3	£269.7
0-17 years old (n = 2,269)	Mean	£99.6	£164.9	-£65.3**	***0-17 years old n = 15)***	£284.3	£156.4	£127.9	£146.3*	-£43.9	£190.2*
	SE	4.193	7.200	8.332		79.011	29.646	84.390	49.543	87.000	85.529
	lcl	£91.4	£150.8	-£81.6		£114.83	£92.9	-£45.0	£49.1	-£214.6	£22.5
	ucl	£107.9	£179.0	-£49.0		£453.76	£220.0	£300.7	£243.4	£126.7	£357.9
18 -44 years old (n = 6,186)	Mean	£151.8	£198.0	-£46.3**	***18 -44 years old (n = 128)***	£323.9	£216.9	£106.9*	£159.1**	£14.8	£144.3**
	SE	5.039	4.978	7.083		39.994	25.600	47.486	35.435	34.067	37.120
	lcl	£141.9	£188.3	-£60.1		£244.7	£166.3	£13.4	£89.6	-£52.0	£71.5
	ucl	£161.6	£207.8	-£32.4		£403.0	£267.6	£200.4	£228.6	£81.6	£217.1
45 -64 years old (n = 4,999)	Mean	£226.8	£271.5	-£44.7**	***45 -64 years old (n = 96)***	£669.4	£295.7	£373.6*	£421.6**	£7.0	£414.7**
	SE	6.444	6.032	8.827		166.659	34.117	170.115	51.295	42.587	54.708
	lcl	£214.2	£259.7	-£62.0		£338.49	£228.0	£38.1	£321.1	-£76.5	£307.4
	ucl	£239.4	£283.3	-£27.4		£1,000.21	£363.5	£709.2	£522.2	£90.5	£521.9

	Patients with GI only (N= 16,822)				Patients with GI and sequelae (N = 286)				Impact of sequelae		
Stratum		**After**	**Before (B)**	**Difference (A-B)**	**Stratum**	**After**	**Before**	**Difference (A-B)**	**After[1]**	**Before[2]**	**DID[3]**
65 years + (n = 3,093)	Mean	£477.2	£529.3	-£52.1**	***65 years + (n = 43)***	£1,248.6	£705.9	£542.7	£768.8**	£165.4	£603.4**
	SE	13.577	12.975	18.779		258.516	122.185	285.936	117.936	108.710	130.561
	lcl	£450.6	£503.9	-£89.0		£726.9	£459.3	-£25.9	£537.5	-£47.7	£347.4
	ucl	£503.8	£554.8	-£15.3		£1,770.3	£952.4	£1,111.3	£1,000.0	£378.6	£859.4
IMD_1 (n = 4,973)	Mean	£199.7	£239.1	-£39.5**	***IMD_1 (n = 91)***	£369.2	£295.2	£74.0	£165.9**	£45.9	£120.0*
	SE	6.208	5.988	8.626		82.164	48.218	95.268	46.217	43.558	51.174
	lcl	£187.5	£227.4	-£56.4		£205.96	£199.4	-£114.0	£75.3	-£39.5	£19.7
	ucl	£211.8	£250.9	-£22.6		£532.43	£391.0	£262.0	£256.5	£131.3	£220.3
IMD_2 (n = 4,335)	Mean	£217.5	£266.0	-£48.4**	***IMD_2 (n = 84)***	£780.7	£390.7	£390.1	£541.1**	£97.5	£443.7**
	SE	7.093	7.088	10.028		192.151	61.254	201.679	56.728	50.415	59.413
	lcl	£203.6	£252.1	-£68.1		£398.6	£268.8	-£8.1	£429.9	-£1.4	£327.2
	ucl	£231.4	£279.9	-£28.8		£1,162.92	£512.5	£788.3	£652.4	£196.3	£560.2
IMD_3 (n = 3,335)	Mean	£240.9	£300.3	-£59.3**	***IMD_3 (n = 49)***	£458.1	£212.4	£245.7*	£189.0*	-£77.6	266.6*
	SE	9.387	9.542	13.385		79.974	32.070	86.165	77.372	77.016	81.409
	lcl	£222.5	£281.5	-£85.6		£297.3	£147.9	£74.7	£37.3	-£228.6	£107.0
	ucl	£259.3	£319.0	-£33.1		£618.9	£276.9	£416.8	£340.7	£73.4	£426.3
IMD_4 (n = 2,585)	Mean	£233.0	£285.1	-£52.2**	***IMD_4 (n = 41)***	£676.9	£347.5	£329.5*	£420.1**	£74.0	£346.1**
	SE	8.954	8.637	12.441		132.392	66.154	148.000	72.738	67.383	77.702
	lcl	£215.4	£268.2	-£76.5		£409.4	£213.8	£35.0	£277.5	-£58.1	£193.7
	ucl	£250.5	£302.1	-£27.8		£944.5	£481.2	£624.0	£562.7	£206.2	£498.4
IMD_5 (n = 1,582)	Mean	£299.2	£359.1	-£59.9**	***IMD_5 (n = 20)***	£776.6	£295.8	£480.9	£495.2*	-£118.8	£614.0**
	SE	16.889	16.204	23.405		415.909	58.883	420.056	157.799	141.223	166.378
	lcl	£266.0	£327.3	-£105.8		-£93.9	£172.5	-£369.5	£185.7	-£395.8	£287.6
	ucl	£332.3	£390.9	-£14.0		£1,647.1	£419.0	£1,331.2	£804.7	£158.2	£940.3

Patients with GI only (N= 16,822)					Patients with GI and sequelae (N = 286)				Impact of sequelae		
Stratum		**After**	**Before (B)**	**Difference (A-B)**	**Stratum**	**After**	**Before**	**Difference (A-B)**	**After[1]**	**Before[2]**	**DID[3]**
CHI_0 (n =11,150	Mean	£136.5	£148.1	-£11.6*	**CHI_0, (n=183)**	£297.6	£147.6	£150.0**	£161.1**	-£0.5	£161.6**
	SE	3.424	2.974	4.535		41.691	14.576	44.166	27.252	23.289	29.276
	lcl	£129.8	£142.3	-£20.5		£215.35	£118.81	£63.18	£107.7	-£46.2	£104.2
	ucl	£143.2	£153.9	-£2.7		£379.87	£176.33	£236.89	£214.5	£45.1	£219.0
CHI_1 or more, (n=5,672)	Mean	£359.3	£396.8	-£37.5*	**CHI_1 or more, (n=103)**	£989.2	£460.4	£528.8**	£629.9**	£63.6	566.2**
	SE	8.672	8.815	12.366		179.056	62.675	189.708	68.693	65.959	75.317
	lcl	£342.3	£379.5	-£61.7		£634.0	£336.1	£154.7	£495.2	-£65.7	£418.6
	ucl	£376.3	£414.0	-£13.2		£1,344.3	£584.7	£902.8	£764.5	£192.9	£713.9

S.E – standard error; lcl – lower confidence limit (95% CI); ucl – upper confidence limit (95% CI); *P <0.05; **P<0.001; After[1] – (Mean cost quarters after for patients with GI and sequelae – Mean cost quarters after for patients with GI infection only) Before[2]-(Mean cost quarters before for patients with GI and sequelae – Mean cost quarters before for patients with GI infection only); DID[3] – Difference in mean differences (After[1] - Before[2])

Sensitivity analysis

In Chapter 5, patients with the previous diagnosis of the conditions of interest were excluded from the overall analysis to reduce any dilution effects in the estimates of incidence. These patients were also considered in a sensitivity analysis for the economic analysis in this chapter by exclusion from the calculation of average quarterly resource use and tests. There were no changes in the average quarterly resource use and costs per patient. Patients with sequelae (both *Campylobacter* and NTS) still incurred significantly higher costs than their GI infection only counterparts in the quarters post-infection (Data not shown).

Secondary analysis

Annual resource use and costs in the five years pre and post-diagnosis of infection were evaluated in a secondary analysis. Patients with GI infection only had a similar pattern of a peak in resource use and costs at -Y1 pre-infection. However, levels did return to baseline (-Y5) by Y5 post-diagnosis across all the different healthcare resource domains except for prescriptions where levels remained elevated (Appendix 7-7 and Appendix 7-8).

All patients with sequelae (both *Campylobacter* and NTS) also had a peak in resource use and costs in the year preceding infection (-Y1). In contrast to patients with GI infection only, levels remained elevated up to five years post-infection (Y5) above what was observed at baseline (-Y5) for tests despite a decline in overall resource use. However, resource use for prescriptions and outpatient attendances continued to increase up to Y5 post-infection (Appendix 7-7 and Appendix 7-8).

7.4 Discussion

7.4.1 Summary of main findings

Sequelae in patients with selected GI infection significantly impacted the direct healthcare expenditure in these patients in the post-infection period compared with costs accrued in the pre-infection period and also compared with patients who had the selected GI infections only. Overall, sequelae of *Campylobacter* infection led to an additional £1,254,723 in NHS healthcare expenditure in England per year, while sequelae of NTS infection was at a lower but significant value of £223,579 annually.

The increased total expenditure in the periods post-infection amongst patients with the selected GI infections and sequelae was stronger in the immediate post-infection period and continued up to Q3 post-infection driven primarily by hospital admissions for HRG subchapter - Digestive disorders and procedures, face-to-face/visit-out-of-hours consultations, and microbiology tests. The increase in microbiology tests was due to a spike in testing in the 28 days following diagnosis, suggesting it may be the same episode of illness. Although only 2% of the total costs were due to colonoscopies, the 7-fold increase in this procedure in the post-infection period suggest these patients were prone to additional investigations, which increased their expenditure. Colonoscopies are not routinely performed in a primary care setting and only warranted in secondary care based on a referral for patients with suspected Crohn's disease or ulcerative colitis [15,16]. Routine colonoscopy surveillance is also performed on people with inflammatory bowel disease or adenomas, who have a higher risk of developing colorectal cancer [17]. Outpatient attendances/procedures were not significantly impacted by sequelae. This may be a consequence of separating colonoscopies, which is one of the main procedures for investigating disorders of the gastrointestinal tract in outpatient settings.

Patients with the selected GI infections only had approximately 10% reduction in total expenditure in the quarters post-infection in comparison with the quarters' pre-infection. Decreases in

consultations (mainly face-to-face and visit/out-of-hours), tests (mostly microbiology tests) and hospital admissions were responsible for the reduced expenditure in the post-infection period for these patients. This is consistent with clinical practice and health-seeking behaviour patterns of patients accessing healthcare, with regular consultations and tests until a diagnosis is reached [12,18]. From this point onwards, healthcare utilisation is likely to decrease for an acute and self-limiting condition such as a GI infection where further investigations and treatments are not warranted.

In the pre-infection period, patients with the selected GI infections only had significantly higher total expenditure driven mainly by hospital admissions, with an increase in the utilisation rates from –Q1 with up to four years post-infection. Although only a third of patients had a CCI of 1 or more at entry into the cohort, prescriptions accounted for over 50% of all healthcare resource utilisation, consistent with other studies [19]. Drugs for the central nervous system, cardiovascular diseases and endocrine disorders remained elevated for all patients at five years post-infection. Of all the tests performed on patients with the selected GI infections only, 70% was for clinical biochemistry, and this includes routine monitoring tests for endocrine disorders. All these suggest the existence of underlying health conditions, which is common amongst patients who access primary health care services [20].

Stratification of total costs by patients age, sex, SES and presence or absence of comorbidities revealed those with sequelae who were older (65 years and above), males, and with a CCI of 1 or more incurred the highest costs. Males of working age usually have different health-seeking behaviour to their female counterparts and may only seek health care more frequently if they have underlying health problems. Comorbidities are common in older age groups, in those who access primary care services with established links to low SES [20,21]. These patients are prone to frequent consultations and further investigations, leading to additional costs.

There was no clear distinction on SES as both those living in one of the affluent areas (IMD-2) and those living in the most deprived areas (IMD-5) had significantly higher costs in the periods

post-diagnosis. Due to the small number of patients with sequelae, it was not possible to further stratify patients based on the type of sequelae as previous studies suggest social patterning in the onset of IBS with those of a higher SES at greater risk, and the opposite pattern for IBD [22,23]. Notwithstanding, Chapter 6 (section 6.5.1) demonstrated that patients living in less privileged areas were less likely to develop IBS if they had a prescription for PPI in the 12-months before their *Campylobacter* infection. Admittedly, it was not possible to determine if the same protective effect will exist in the absence of PPI.

Given the type of data used in this study, the focus of this thesis was on the economic impact from the perspective of the payer, the NHS. Nonetheless, it is important to acknowledge that the NHS costs are only part of the overall burden of *Campylobacter* and NTS infections because there are other wider societal costs associated with these GI infections. Previous UK studies, using published cost estimates from IID1, reported costs to patients [24]. These include direct, out-of-pocket expenses resulting from the GI illness, such as medications, transport to health clinics, childcare, cleaning products, special foods, and indirect costs such as loss of employment [24,25]. These costs accounted for 80% of all economic costs following *Campylobacter*, and two common viral infections (norovirus and rotavirus)[24]. Applying this estimate to the findings of my work, sequelae of *Campylobacter* would cost both patients and NHS £6.3 million 95% CI (£4.4 million, £8 million). Still, this would not fully capture the impact of all sequelae of *Campylobacter* infection as only GBS as a sequela was considered in the study. Research from the Netherlands demonstrated that IBS lasting for up to five years following *Campylobacter* infection produced a cost of €28.9 million (discounted at 4%) to patients, healthcare provider and the wider society [26]. This cost accounted for 38% of all costs attributed to *Campylobacter* infection with indirect non-health care costs such as absenteeism and associated loss of income/productivity as the significant drivers inflating the cost [26]. Hence, if absence from work precisely due to sequelae were included in the cost estimates generated in this thesis, the cost implications of the loss of income/productivity to

both employees and employer would be much higher than the £6.3 million estimate above for *Campylobacter*.

In the GP case-control study component of IID1, NTS patients reported, on average a higher number of days off work in comparison with *Campylobacter* patients (9 vs 6). In the IID2 study instead, absence from work for 1-2 days was reported in over half (62%) of all patients with any GI infection (n = 818) with a small proportion (8%) reporting an absence of over five days [25,27]. Sickness absence by pathogen and resulting sequelae were not available in the IID2 study, limiting inferences for the estimates produced in this thesis. However, there was a clear link between absenteeism and severity of infection in the IID2 study [27]. It is well documented that patients who seek healthcare for their GI infection are usually at the severe end of the spectrum of infection [14,28].

Sequelae of *Campylobacter* and NTS infections can also have a considerable impact on food production. Source attribution models to partition the burden of human food-borne disease to specific sources, including animal reservoirs and vehicles such as food, have been developed by various researchers [29]. In one of such studies assessing the five major transmission pathways of GI infections (foodborne, environmental, direct animal contact, travel-associated and human to human spread), the researchers found that up to 40% of these infections were attributed to food only; making contaminated food the single most crucial transmission pathway [30,31]. When food types were further divided into 11 groups, poultry meat and eggs were the significant vehicles attributed to *Campylobacter* and NTS infections, respectively [30,32]. This has significant cost implications for the agriculture and food industry.

Efforts to prevent contamination of food along the food chain are crucial in prevention and maintaining public confidence in the food that ends up on their plate – all of which come at a cost. During the rise of *Salmonella* Enteritidis PT4 in the UK, outbreak investigations provided evidence of its links to raw shell eggs in 1988. By 1989, following a statement by a Junior Health Minister

in a British television interview that "Most of the egg production in this country, sadly, is now infected with Salmonella," the sale of eggs plummeted by 60% almost overnight with continuous decline in sales by around 8% per year over the next 10 years, which was a disaster for the industry [33]. Following this, the British Egg Industry Service introduced a stringent new Code of Practice – The Lion Mark at an estimated cost of £4 million [33]. The Code of Practice included mandatory vaccination of all pullets destined to lay Lion eggs against *Salmonella*; full traceability of hens, eggs, and feed; and a "best-before" date stamped on the shell and pack, in addition to on-farm stamping of eggs and packing station hygiene controls [34]. Eggs are stamped with a "Lion Mark" indicating they have been produced in adherence to UK and EU law and the Lion Quality Code of Practice by subscribers to the British Egg Industry Council [33,35].

It is estimated that these measures may have prevented ~904,000 cases of NTS illness in the community (225,973–20,247,145) ~6,300,000 days of illness, ~26,000 hospitalisations, and ~2,000 deaths since 1998 [36]. The cost of the vaccination program (including Lion sampling and testing) was estimated to be around £52 million as of 2012 [33]. This also increased confidence in British eggs production and therefore consumption, and Lion eggs now account for around 85% of the total market [33]. Within the retail sector, the market share of Lion eggs rose from approximately 60% in 1998 to 95% in 2010. Further, in 2017, the FSA confirmed that Lion eggs are the only form of eggs that are safe to consume runny or raw by vulnerable people such as pregnant women, the very young and elderly, following a report by the Advisory Committee on the Microbiological Safety of Food on the risk of microbial contamination of eggs and their products [37] [38].

Levels of *Campylobacter* in retail poultry in the UK are now (as of 2018) within the stipulated target of below 10% since testing began in 2014, however continuous efforts by government and industry are still warranted [39]. In New Zealand, successful industry-wide interventions introduced between 2007 and 2008 in reducing contamination of poultry meat led to a substantial saving of NZD 57

million in total cost (incorporating industry costs) following a 58% reduction in cases of *Campylobacter* infection and decline of GBS [40].

7.4.2 Strengths and limitations

Strengths

This is the first study to evaluate the impact of *Campylobacter* and NTS infections and their associated sequelae on healthcare resource utilisation and costs using linked routinely captured primary care and hospital data on a cohort of patients with these GI infections. Hence observations are based on patterns of care for a large and representative group of patients treated in real-world settings. This provides a unique opportunity to follow a patient's journey across the NHS and to calculate more precise estimates stratified by patient-level demographic factors, central to personalised medicine.

Previous cost estimates on GI infections in the UK, Belgium, The Netherlands, and Australia focused on the total cost of illness of GI infection without a measure of the absolute difference in quarterly/annual utilisation for the periods before and after infection which is central to economic evaluation [24,41]. In the UK study, only GBS was considered as a sequela of *Campylobacter* infection. Cases were selected from several standalone data sources such as a GP presentation cohort study, outbreak surveillance data, and HES APC data without linkage of individual patient's record [24]. Therefore, it was not possible to follow a patients' health journey across the NHS or stratify resource use and costs by patients' demographics [14,24,42]. Also, heterogeneity could have impacted the estimates with the outbreak surveillance data. Outbreak surveillance is a voluntary system prone to reporting bias as those affecting a defined cohort of people are more likely to be identified and investigated than those that are widely dispersed in the community.

Limitations

Studies have demonstrated the decline in GI infection related GP consultations, with a rise in patient-led care [14]. Hence, the impact of sequelae following the selected GI infections in this thesis may be underestimated.

Although one of the richest datasets available on patients' medical history was used for the analyses, the definition of index date/date of diagnosis of infection may have inflated the costs in the pre-infection period. This is because patients with the selected GI infections only had elevated tests and consultation rates from two weeks pre-infection up to a week post-infection. As previously described in Chapter 4, the index date can only be derived if patients are followed up before disease onset in a traditional cohort design or a randomised controlled trial. In the absence of this, date of specimen/date of consultation can be adopted as a proxy date for onset of illness.

Other data sources that capture medical encounters include Accident and Emergency (A&E) data from HES. This data was not included due to its poor quality and limited availability (i.e. from 2007 onwards only). Excluding this data would mean our cost estimates are conservative as A&E attendances are classified as non-elective patient care attracting a high unit cost.

Patients in the cohort entered at different time points. The version of the cost grouper software used in this thesis was implemented for reference costs attached to HRGs from 2007/2008 onwards, based on the fourth revision of HRG. No comparisons was made on the effects, if any, of using the 2006/2007 cost grouper based on HRG version 3.5. The main change in the HRG classification from HRG3.5 to HRG4 is the increase in the number of HRGs that have zero cost and changes in the way non-elective costs are reported [6]. HRG4 introduced unbundled HRGs, which leave some (core) HRGs with zero cost since the cost associated with that episode is recorded separately [6,43]. This increases the number of HRG4 codes with zero costs in comparison with HRG3.5. To overcome this, spells with unbundled HRGs were also costed and incorporated into the total costs.

The exact costs for each patient's specific care across the various domains of healthcare were attached. However, this is from a payer's perspective and does not include direct estimation of costs borne by individuals such as direct, out-of-pocket expenses resulting from illness, such as medications, transport to health clinics, childcare, cleaning products, special foods etc., and indirect costs of lost income by patients themselves or by caregivers. Wider societal costs from illness in caregivers and costs of lost productivity to employers and the wider economy were also not included. Hence, the cost estimates are underestimated as incorporating these costs would inflate the costs in the post-diagnosis period as discussed earlier.

7.4.3 Conclusion

Patients with *Campylobacter* and NTS infections who later develop sequelae significantly impact the NHS by approximately £1,254,723 and £223,579 in increased annual healthcare expenditure, respectively. The increased expenditure impacts all domains of healthcare resource. Males, people aged 65 years and above and those living with existing comorbidities incurred the highest costs.

Patients with these GI infections only may also have underlying health conditions due to the overall high rate of prescriptions even at five years post-diagnosis. This may explain the lack of association with CCI and the onset of IBS amongst patients with a PPI prescription in the 12 months before *Campylobacter* infection (section 6.6.4).

This chapter further highlights the importance of ascertaining the index date of infection due to the elevated levels of tests up to 2-weeks before the index date adopted for this thesis. Despite the limitations, the cost estimates presented here can inform input parameters in decision analytical models of cost-effectiveness of future healthcare or industry interventions to reduce the overall burden of *Campylobacter* and NTS infections.

The implications of the findings presented here in relation to the overall aims and objectives of this thesis will be discussed in Chapter 8.

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Chapter 8

Discussion

8.1 Overview

This chapter summarises the main research findings from the studies presented in this thesis. It discusses the strengths and the limitations of the individual studies in Chapters 3, 5, 6 and 7, the data sources, and the study design (Chapter 4). The implications of the findings for clinical practice, and public policy are outlined, and suggestions are made for future research. The overall conclusion of the thesis is stated at the end.

This thesis aims to identify the gaps in the literature in the sequelae of *Campylobacter* and NTS infections globally, provide a comprehensive analysis of the incidence of sequelae following these infections, the associated modifiable risk factors, and the economic impact on the NHS in England between 2000 and 2015.

The research undertaken included four studies. The first was a systematic review and meta-analysis of the reported incidence of sequelae of the selected GI infections. The second was a population-based study to determine the incidence of sequelae following the selected GI infections. The data source was deterministically linked individual patient primary care records from the Clinical Practice Research Datalink (CPRD), hospital records from Hospital Episode Statistics (HES), mortality records from the Office for National Statistics (ONS) for England, and socioeconomic status from the English Index of Multiple Deprivation version 10 (IMD-10). Additionally, individual patient's laboratory data from Public Health England's Second-Generation Surveillance

System (SGSS) were linked to HES, ONS mortality records, and IMD-10. The third study used the linked primary care records to assess the association of taking antibiotics or proton pump inhibitors (PPI) and the onset of sequelae following the selected GI infections. The fourth and final study was an economic assessment of the resource use and costs associated with sequelae of the selected GI infections using the linked primary care records.

8.2 Main findings of my thesis

Based on the systematic review, the incidence of IBS was reported in *Campylobacter* (0% to 18%) and NTS (0.0% to 37.9%) patients, while post-infectious ReA was reported in up to 63% of the patients with either *Campylobacter* or NTS infections. The estimates were not pooled as included studies had a high level of heterogeneity. For the population-based study, diagnosis of sequelae was recorded in CPRD-linked (1.7%, 347/20,471) and SGSS-linked (0.4%, 1,378/353,892) datasets following the selected GI infections. Overall, the detection of post-infectious sequelae was more sensitive using the CPRD-linked data as conditions such as IBS and ReA which are commonly diagnosed in primary care were captured as well as diagnoses recorded in HES in comparison with the SGSS-linked data which was limited to diagnoses recorded in HES only. This is further reflected in the different rates of onset of sequelae that was recorded from these datasets. The mortality rate was low from both CPRD-linked and SGSS-linked datasets. However, where death was recorded, it was linked to NTS as the preceding infection.

Of the primary sequelae of interest (ReA and IBS), IBS was frequently recorded across both data sources but with a higher proportion in the CPRD-linked data (73.2%, 254/347) in comparison with SGSS-linked (50.0%, 678/1,397). When the rate of onset of sequelae for each GI pathogen was considered using CPRD, IBS following *Campylobacter* was greatest within the first three months post-infection (14.6 per 1,000py, 95% C.I (11.4 - 18.6)), while *Campylobacter* triggered ReA was

greatest within 1-month post-infection (4.1 per 1,000 py, 95% C.I 1.8 - 9.0) and up to 3-months post-infection for NTS patients (7.5 per 1,000py, 95% C.I 3.1 - 18.0). However, the rates of onset of ReA between the two GI pathogens were not significantly different due to wide confidence intervals for NTS patients. This may be due to smaller numbers of NTS patients in comparison with *Campylobacter* patients, thereby limiting precision and any inferences on differences in sequelae rates between the two patient groups.

Although overall sequelae rates were higher using CPRD-linked data in comparison to SGSS-linked data, the rate of recorded diagnoses for the secondary sequelae of interest (UC, CD, RA, GBS) was greater in the SGSS-linked data (48.5%, 678/1,378) in comparison with CPRD-linked data (26.8%, 93/347). Within 12 months post-infection, the rate of onset of UC following *Campylobacter* infection (0.7 per 1,000 py, 95% C.I (0.6-0.8)) was significantly greater than the rate of all other secondary sequelae onset following *Campylobacter* infection.

A higher proportion of females had diagnoses for the sequelae of interest across both datasets. NTS patients from both datasets and *Campylobacter* patients from SGSS who developed sequelae were older than their GI infection only counterparts, while there were no differences in age amongst *Campylobacter* patients with or without sequelae from CPRD. This age and sex patterning amongst patients with sequelae may reflect the health seeking behaviour of patients who are most likely to have a recorded diagnosis for sequelae. Hence, it may be a potential ascertainment bias. For instance, women between the ages of 16-60 have 30% more consultations than their male counterparts and reproduction alone does not account for the differences [164]. As heavy users, they will be more likely to have subsequent consultations leading to the increased recording of sequelae. However, no regional differences or patterning of IMD deprivation were observed between patients with sequelae and those with the selected GI infections only across both datasets.

The role of modifiable risk factors which include the use of antibiotics or PPI in the onset of sequelae was assessed in both the population-based study using selected *Campylobacter* patients

from the CPRD-linked data (Chapter 6) and in the systematic review (Chapter 3). Over a third of patients (36%) had a prescription for antibiotics in the seven days pre- and post-infection with no apparent association between antibiotics usage and all sequelae considered. Of the seven studies which assessed the association between antibiotics and development of ReA amongst patients with the selected GI infections in the systematic review, there was no clear association in the risk of ReA onset.

Although fewer patients received PPI (26%) in the 12 months before infection, in comparison to patients receiving antibiotics in the CPRD-linked data, there was an elevated risk for the onset of IBS amongst those with a PPI prescription. Females and those below the age of 65 years had the greatest risk and were two and a half times more likely to develop IBS following a *Campylobacter* infection while on prior PPI prescription (aOR 2.5, 95% C.I 1.9, 3.4). When patients' SES was considered, those living in less affluent areas (IMD – quintiles 3 and 4) who had prescriptions for PPI where less likely to develop IBS. The same direction and magnitude of risk were reported in the only study that assessed the role of PPI in the onset of ReA following *Campylobacter* and NTS infection in the systematic review.

Subsequent development of sequelae in patients with *Campylobacter* infection significantly impacted the NHS with an additional £1,254,723.0, 95% CI (£881,561.0 , £1,785,827.0) in annual healthcare expenditure, while for NTS patients, a lower but significant impact was observed, £223,580.0, 95% CI (£92,058.0, £542,920.0) annually. The increased expenditure was observed across all domains of healthcare resource except for outpatient attendances/procedures. Males, people aged 65 years and above, and people with existing comorbidities incurred the greatest costs.

8.3 Strengths and limitations

The strengths and limitations of all studies in the thesis and the methodological critique are presented here.

8.3.1 Strengths

The systematic review conducted was the first published review to assess the existing evidence for the role of antibiotics and PPI in the onset of sequelae of *Campylobacter* and NTS infections. Previous systematic reviews only assessed the risk factors in the onset of IBS, IBD and ReA without considering the interplay of modifiable factors and GI infections in the incidence of these conditions. The systematic review conducted in this thesis highlights the need for more primary studies to elucidate the role these medications may have on the onset of post-infectious sequelae.

The overarching strength of this thesis is the linked data for all empirical studies. The combination of individual patient-linked records across all the main healthcare access points in England indicates that patients selected from these datasets sought care for their *Campylobacter* and NTS infections. Consequently, their medical encounters enabled focused study definitions, design, and analysis tailored to address gaps identified in the systematic review, while allowing a complete economic assessment of the direct healthcare use and costs following sequelae of the selected GI infections.

CPRD is prospectively collected, eliminating recall bias (the presence of a disease outcome affecting the reporting of the exposure status) amongst patients. The linkage to HES allowed the identification of patients who were hospitalised for the selected GI infections, which could not be gleaned from CPRD records only. Further analysis on the temporal association between sequelae onset and diagnosis of the selected GI infections identified patients who had an ICD-10 code for the sequelae of interest up to a month before the index date for the selected GI infections in HES without a corresponding Read code for the sequelae in CPRD. For such patients, the first record

of a Read code for the sequelae following the index date for the selected GI infections recorded in CPRD was not an indication of incidence. Instead, it was the prevalence of these conditions that were measured. If CPRD alone was used, misclassification of prevalent cases as incident cases might have occurred. Further, it permitted the stratification of all direct healthcare use and costs following a patient's health journey across primary and secondary care in England. This direct estimation provides more robust and reliable estimates that reflect real-world clinical settings.

The SGSS-linked data allowed the direct estimate of the incidence of the studied sequelae following GI infections — this is a first for England. In the absence of CPRD data for risk factor information, SGSS-linked to HES is a useful source for hypothesis generation.

8.3.2 Limitations

The overarching limitations of the thesis mostly arise from its reliance on historical data collected for clinical purposes and not research. The Accuracy of clinical investigations, diagnoses and coding were central to data validity.

Selection bias

For the CPRD-linked data set, the first recording of diagnosis specific for *Campylobacter* or NTS infection was used for patient selection. Since both infections are common, it can be challenging to determine the first presentation of these infections in patients. Moreover, the case definition for patients was based on sensitive Read codes following consultation for *Campylobacter* or NTS infections. This is subjective to GP behaviour during the consultation before and after the diagnosis of infection. Not all GPs follow the stipulated guidelines in requesting stool culture from patients presenting with symptoms of gastroenteritis, and when they do, they might not all enter the Read code for the identified pathogen and may use a broad code for "gastroenteritis" [165]. GPs are more likely to request a stool culture if the patient reported foreign travel or have severe symptoms such as bloody diarrhoea or prolonged diarrhoea [109,165].

The CPRD does not contain information on over-the-counter medication. PPIs are readily available over the counter; therefore, the effect of the onset of IBS amongst *Campylobacter* patients may be underestimated if the patients who do not have a PPI prescription in CPRD use over-the-counter PPI.

Misclassification and information bias

All exposure and outcome measurement centred on the definition of the index date. The specimen date in SGSS and date of diagnosis of infection in CPRD were adopted as the index date. Classification of index date is an inherent limitation for medical records research. Patients usually present with symptoms before receiving a diagnosis. However, they are not always captured systematically within CPRD as some are recorded as free text. All patients with sequelae who had a previous diagnosis of the conditions of interest before the index date were excluded to limit the misclassification bias in the differentiation of prevalent cases from incident cases (section 5.4). Hence estimates of sequelae in this thesis may be underestimated.

An alternative approach to improve the definition of the index date is the assessment of any temporal association between symptoms, tests, and date of diagnosis to determine if an earlier date before the recording of diagnosis could be adopted as the index date. However, this was not feasible within the scope of this thesis.

The measure of SES may have also introduced misclassification bias. I used IMD, a small-area level indicator of deprivation, and not an individual level measure of a person's socio-economic circumstances. This could result in misclassification of an individual's deprivation status. Therefore, the observed association between deprivation level and sequelae onset following *Campylobacter* infections may not be the true reflection of the influence SES may have on the development of sequelae.

Confounding

Confounding by indication, which cannot always be measured directly, may have occurred in the assessment of the effect of PPI usage in the onset of IBS following *Campylobacter* infection. It occurs when the underlying reason for exposure is also a risk factor for the outcome. Admittedly, the reason for PPI prescription was not assessed. Therefore, the PPI-IBS relationship observed amongst *Campylobacter* patients may be caused by the underlying reason for the prescription. Indeed, a systematic review and meta-analysis reported an 8-fold risk in the prevalence of IBS in patients with functional dyspepsia (FD) compared with patients without this condition [166]. However, there was a high level of heterogeneity in the included studies with varied reported estimates of the conditions depending on the definition adopted. Patients with FD do not have structural abnormality and can be prescribed PPI to help alleviate their symptoms.

Nevertheless, peptic ulcer, which is another indication for PPI use, was included in the calculation of the CCI; and including the CCI in the logistic regression model, did not show any association with sequelae onset. Other techniques to address this may be through controlling for the presence of other functional gastrointestinal disorders in the logistic regression model, or the use of propensity score matching where patients with similar characteristics are assigned a score and only patients with similar scores are assessed for the effect of PPI on IBS onset. However, restricting the sample to a particular class of patients will reduce the external validity to a wider patient group.

Another potential confounding mechanism that may have impacted the observed effect of antibiotics usage and onset of IBS is confounding by severity of illness. This is comparable to confounding by indication in that patients receiving antibiotics for their GI infection are more likely to have severe illness in comparison with those who do not, thus making them systematically different from those who did not receive treatment for their infection. Measuring disease severity is difficult, with retrospective real-world data. A proxy measure for this is hospitalisation. However, a higher proportion of the cohort (34%) received antibiotic treatment in comparison with those

that were hospitalised (4.2%). Hence, this would not have affected the reported estimate onĵ the risk of IBS if hospitalisation was included in the logistic regression model.

External validity

The inclusion criteria for all studies required a diagnosis of *Campylobacter* and NTS infection. Studies have demonstrated a decline in GI infection related consultations in primary care with suggestions of an increase in patient-led care [112]. Also, amongst patients who consult and submit a sample for laboratory testing, up to 60% of samples may not yield the GI pathogen [167]. However, this did not influence the estimated incidence of sequelae, as only diagnosed cases were included in the denominator.

Patients' demographics in the CPRD-linked data were comparable to the entire CPRD population, which is a nationally representative data source, and to SGSS national surveillance data of *Campylobacter* and NTS infections. Hence, the ascertainment ratios from IID2 which measure the level of underreporting between GI infection-related consultations captured in primary care and the level of IID in the community can be extrapolated to determine the incidence of sequelae of the selected GI infections in the community (section 2.2.5). Such extrapolated estimates may require correction/adjustment for differential rate in the incidence of sequelae amongst confirmed and undiagnosed cases of *Campylobacter* or NTS infections, as confirmed cases of these GI infections may have a higher rate of sequelae than undiagnosed cases leading to an overestimate of incidence of sequelae following these GI infections in the community.

8.4 Research in context

8.4.1 Incidence of sequelae following *Campylobacter* and NTS infection

The proportion of patients with a recorded diagnosis for IBS following *Campylobacter* or NTS infections was higher than previously published estimates based on retrospective studies of

medical records with a large number of patients (> 10,000). The studies reported a similar proportion developing IBS regardless of the GI pathogen (NTS, 0.01-1%; *Campylobacter*, 0.03-0.89%) [168,169]. In contrast, a higher proportion of NTS patients were diagnosed with IBS from CPRD (NTS, 1.9%, 51/2,633; *Campylobacter* 1.1%, 203/17,838).

When follow-up was considered, the incidence of IBS in *Campylobacter* patients was approximately 6-fold higher than the reported incidence of IBS in the absence of GI infections (~ two per 1,000 person-years) for studies using medical records and selecting only first diagnosis of IBS within 12 months of follow up [143]. Moreover, the rate of onset was highest within the first 3-months post-infection. This is contrary to the Rome III and more recent Rome IV criteria for the diagnosis of IBS, which states that symptom onset should occur at least six months before diagnosis and symptoms should be present during the last three months [170]. This criterion significantly reduced the heterogeneity of the included studies for post-infectious IBS in the systematic review (section 3.4.2).

Similar to other studies, there was no GBS following NTS infection in the cohort studies using both CPRD-linked and SGSS-linked data [97]. Estimates of *Campylobacter*-related incidence was low in the cohort compared with an earlier study using GPRD data in the UK (0.26 per 1,000 py at three months follow up vs 1.17 per 1,000 py at 60 days follow-up) [40]. Although the study included patients with *Campylobacter* infection for the years 1991-2001, while this study was conducted at a time when overall GI-related consultations in primary care had reduced (2000-2015), this should not have impacted the estimates as the overall rate of *Campylobacter* infection has remained stable over both periods.

The incidence of UC and CD was low in both primary care and national surveillance records. This agreed with the systematic review conducted in this thesis and other studies [97]. Some argue that it is the existence of these conditions that increase the risk of GI infections, or the diagnosis of incident infections, and not the reverse; while one study reported an increased risk with the onset

of UC and not CD [171,172]. However, the authors included both self-reported episodes of GI infection and CD and follow-up varied amongst patients in the cohort [172]. Moreover, it was a cohort of military personnel with an over-representation of men, who reported life stressors such as anxiety and depression, and some had a history of IBS. These are factors that contribute to an elevated risk of UC [172].

8.4.2 Factors associated with the onset of sequelae following *Campylobacter* and NTS infections

The association of PPI or antibiotics usage in the onset of sequelae of *Campylobacter* or *NTS* infections were assessed in both the systematic review conducted (Chapter 3) and in the cohort study (*Campylobacter* infection only) using CPRD-linked data (Chapter 6). *Campylobacter* patients with a PPI prescription (26%) within 12 months prior to their GI infection had an elevated risk in the onset of IBS; adjusting for any effects of age and sex increased the elevated risks by 50% (OR 1.5, 95% C.I 1.1-2.0; aOR 2.1, 95% C.I 1.5.2-9). Further analysis of the association between age and sex and the onset of IBS amongst *Campylobacter* patients on PPI indicated females below the age of 65 had the greatest risk of IBS. This supports existing evidence on known risk factors for IBS irrespective of a GI infection. Approximately 50% of patients first present before the age of 35 and prevalence is 25% lower in those aged 50 and above in comparison with younger patients [59,143]. Moreover, most adverse events following PPI usage are usually reported in those aged 65 and above; over half (55%) of all new PPI prescriptions were for patients below 65 years of age (mean age 54.2 years sd, 16.3), which is similar to the pattern of *Campylobacter* patients in the cohort who received PPI (mean age, 59.0 years, sd (15.3) [173,174].

Further, there were no significant interactions between having a PPI prescription and age or PPI prescription and sex suggesting the risk of IBS amongst *Campylobacter* infections is even across age and sex. Hence the observed risk of IBS amongst female patients below the age of 65 is as a result of the antecedent *Campylobacter* infection amongst PPI users irrespective of age. This is a novel

finding, with the same direction and magnitude of risk as reported in the only study identified in the systematic review, which assessed ReA onset following the use of PPI in patients with *Campylobacter* or NTS infection [97]. As previously explained (Chapter 6, section 6.6.1), PPI inhibits H+/K +-ATPase activity in the stomach by blocking all three proton pump channels leading to impaired gastric acid secretion which increases the pH to a level that favours pathogenic bacteria such as *Campylobacter* [113,114]. *Campylobacter* infection leads to disruption of the microbiota through mucosal invasion, impaired neuromuscular and immune regulation while pH disruptions in the gut increase the passage of the pathogens into the intestines, which can trigger IBS [114,115].

Antibiotic usage was high in the cohort (34%). Most studies measuring antibiotic usage within primary care in the UK do not usually report antibiotic usage following GI infections as respiratory infections, and urinary tract infections represent the greatest burden of acute infections hence early guidance for antibiotic usage targeted these infections with more recent guidelines advising clinicians not to treat GI infections [175]. In the absence of UK data, a study in the Netherlands using primary care data reported occasional use with only 1 in 11 receiving a prescription for any GI infection in 2013-2014 [176].

Despite the high usage of antibiotics amongst patients in the cohort, there was no association with the onset of sequelae. In the systematic review, the role of antibiotics in the onset of ReA was not clear. Of the seven studies assessing the role of antibiotics in the onset of ReA, only two were conducted on *Campylobacter* patients. One reported an elevated risk without any information on the class of antibiotics, while the other study did not find any association with quinolones, B-lactams or macrolides, despite high usage of antibiotics (83%) amongst patients in the study (Chapter 3, Table 3-4). Of the remaining five studies, four reported fluoroquinolones as the class of antibiotics in treating the NTS patients in each respective study. Two of the studies reported an elevated risk; one reported no association and two, a protective effect that was not significant.

Antibiotic dosage and virulence of the selected GI pathogens were not assessed in the logistic regression model. These factors were shown to contribute to the development of HUS following STEC O157. Also, an elevated risk was observed in cases who had a prescription in up to 2-5 years before the diagnosis of CD in a GPRD based study [177]. Prior GI infection was not assessed in the study, and there was no dose-response relationship. Moreover, there was a similar level of risk associated with the prescription of oral contraceptives, neurological, and cardiovascular drugs [177]. This suggests the observed association may be non-causal but a reflection of healthcare usage among cases. This further supports the hypothesis that the diagnosis of CD in patients with prior GI illness may be due to a detection bias and a reflection of patients' health-seeking behaviour which can lead to increased stool testing. This was evidenced by similar temporal risk patterns for IBD in both patients with stool culture positive and negative tests for both NTS and *Campylobacter* [171].

8.4.3 The economic impact of sequelae of gastrointestinal infections

Chapter 7 presents the first economic assessment of the impact of sequelae of *Campylobacter* or NTS infections on the NHS in England. In the absence of controls without the selected GI infections, patterns of health resource use in the periods before GI infection were similar levels reported in the general population [132]. Patients in the cohort had a higher healthcare utilisation across all domains of healthcare in the periods after their diagnosis date with the prescription rate remaining elevated up to 5 years post-infection. The same pattern was also observed amongst patients with the selected GI infections and sequelae but at a significantly higher rate.

Published cost of illness studies in the UK, The Netherlands and Australia suggest *Campylobacter* patients incur more costs than NTS patients with direct healthcare costs accounting for 20-24% of all the total costs incurred [51,178,162]. The remaining 76-80% of the total costs incurred were indirect non-healthcare related costs such as productivity losses, most especially absence from paid work. These cost estimates where not incorporated in the analysis as the focus was on direct costs to the

payer. However, if the UK estimate of 80% were applied to the findings of my work, sequelae of *Campylobacter* would cost both patients and NHS £6.3 million 95% CI (£4.4 million, £8 million). Still, this would not fully capture the impact of all sequelae of *Campylobacter* infection as only GBS as a sequela was considered in the UK study. The Netherlands study, incorporating sequelae estimates, found that IBS was responsible for 38% of the total costs of *Campylobacter* infection and 76% of the costs associated with sequelae amongst *Campylobacter* patients while for NTS infections, it was 37% of the total costs and 89% of the cost associated with sequelae [178].

The total cost of illness of *Campylobacter* infection is high in the UK [51]. However, estimates for the impact on the NHS of a *Campylobacter* infection suggests, the infection did not significantly increase expenditure in the quarters after infection (-£19.4, 95% C.I (-£30.44, -£8.38), P <0.001). This is because patients with the selected GI infections only had a higher expenditure in the quarters preceding the index date driven by increased consultations and testing. Once these patients receive a diagnosis, their healthcare usage decreases, leading to a decrease in expenditure in the quarters after infection. Conversely, patients who developed sequelae have a significantly higher expenditure in the quarters after the diagnosis of the selected GI infections. For every case of *Campylobacter* with sequelae, approximately £330 extra in expenditure is incurred per quarter. Although the frequency of sequelae may be low, the overall impact on the NHS is significant, at ~£1.3 million annually.

Stratification of resource use and costs by patient age, sex and SES highlighted which patient groups are most likely to incur significantly higher healthcare costs associated with increased utilisation. This was lacking in previous estimates, hence a lack of understanding of which patient groups require certain healthcare resources and when they do, may have hindered the provision of an equitable service by the NHS. Patients aged 65 and over, males, and those with existing comorbidities who developed sequelae incurred the greatest cost in the quarters after diagnosis of

their *Campylobacter* or NTS infection. Older age and living with comorbidities are patient characteristics linked to increased healthcare utilisation and costs [140].

Comparing healthcare resource use and costs to the risk of sequelae, it appears the patients at risk of developing IBS following *Campylobacter* infection (young female patients) are not the ones who consume the most resource or accrue the most significant costs. This may be because their diagnosis did not produce the same level of need for service use in comparison with those who have a higher propensity to access healthcare such as older patients and those with existing comorbidities.

8.5 Implication of findings

8.5.1 Methodological implications

Observational studies using large population-based databases are increasingly used to establish causality and confirm results of RCTs in real-world settings. CPRD is contributing to this as it allows the inclusion of more complete patient data rather than the more restricted groups involved in trials. CPRD and HES for epidemiological and healthcare service research capture real clinical practice rather than the rigorous inclusion and exclusion criteria applied to experimental study designs. This means the findings from these data sources can be directly translated into primary and secondary care settings.

Studies using CPRD-linked data should consider multiple sample size calculations for the linked dataset as the sample size decreases when data is linked since not all patients in one data source will be linked to another. This can affect the validity of the outcomes as power may reduce, especially if both exposure and outcomes are rare. In such instances, investigators can increase the number of years of follow up to increase the sample size. Further, in the absence of a direct link

to a disease registry, comparing patients in CPRD to an existing disease registry such as SGSS allows further comparison of patient's characteristics at baseline.

Although CPRD diagnoses codes have been validated and shown to have a high positive predictive value, most studies still need to develop their algorithms for case selection. The publication of clinical codes in a repository can allow the reproducibility and comparison of studies [179,180]. For instance, all tests were considered and categorised according to their batch testing groups to reflect clinical practice; other studies examining all tests for direct costing can adapt the categorisation to their research questions.

The methods adopted in this thesis are applicable to different disease areas beyond infectious diseases. For exposure and outcome measurements, using CPRD-linked data will provide improved identification of incident cases from prevalent cases, thereby reducing misclassification bias in the estimates of incidence. The CPRD-linked data also allows assessing healthcare use and associated costs prior, for example, to the introduction of a new drug, tests, procedure, vaccines, and other health interventions, and such information can be used to inform cost-effectiveness and other economic modelling studies.

8.5.2 Clinical implications

Female *Campylobacter* patients with PPI prescriptions in the 12 months before their GI illness were 2.5 times more likely to develop IBS. This highlights the need to consider IBS as a negative consequence of *Campylobacter* infection amongst PPI users below the age of 65.

About a third of *Campylobacter* patients in primary care were prescribed antibiotics despite guidelines not to treat unless patients are systemically unwell. Only a minority of patients required hospitalisation for their GI infection, suggesting there was limited evidence of systemic illness. Besides, the recommended antibiotic was not frequently prescribed. Although I did not find specific associations with sequelae onset, this high level of antibiotic use is still a striking finding

in the context of antimicrobial resistance and appropriate prescribing. It suggests a need for improved antibiotics guardianship to ensure patients only receive antibiotics when it is indicated with the right antibiotics prescribed.

8.5.3 Public policy implications

There was a high prevalence of sequelae amongst patients in the SGSS-linked dataset. This linkage can be incorporated into the routine surveillance of GI infections as continuous monitoring may reveal trends in the incidence of sequelae that can warrant further investigations. In the absence of clinical information on risk factors, only hypothesis generation will be possible. Nevertheless, the current practice of whole genome sequencing can elucidate potential virulence factors in GI pathogens and their propensity to cause sequelae.

With the increasing public awareness of self-management of self-limiting illnesses such as *Campylobacter* and NTS infections, it is crucial the consequences of these GI infections are included in any public awareness messages as risk perception of these sequelae may be low.

8.5.4 Future research

Investigating sequelae of GI infections and other acute infections

This thesis worked within the limitations of historical routinely-collected data, by selecting a representative study population, and by defining a case of *Campylobacter* and NTS GI infections within the context of the available data and its clinical and historical context. Since *Campylobacter* infections are common, recurrent GI infections can contribute to sequelae development. This can impact the estimate of the incidence of chronic onset sequelae such as IBS and IBD. A self-controlled case series where patients act as their controls can be adopted to address these questions. It will eliminate heterogeneity between patients and any time-invariant confounding as individual specific risks such as age, sex, ethnicity, and deprivation are controlled, while exposure history is fixed, and events are random. Patients with the first recording of IBS/IBD who have a diagnosis for *Campylobacter* infection can be followed up. The first and repeat diagnosis of

infections at pre-determined intervals before and after the recording of IBS/IBD can be measured. If levels of risks of IBS/IBD are elevated following exposure to GI infection in the periods before the recording of IBS/IBD, this will further elucidate the timing of these conditions following exposure to *Campylobacter* infections. This can also be repeated for other infections such as respiratory infections which are also linked to other forms of sequelae.

Unanswered questions

The ability to study the relevance of modifiable mechanisms such as PPI usage in any causal association in the onset of IBS in *Campylobacter* patients in this thesis was limited. There is a need to assess if a dose-response relationship exists with PPI in *Campylobacter* patients who develop IBS and those who do not as this may help to establish causality. Other questions that may further unravel the relationship between *Campylobacter* patients, PPI and IBS include: is there an existing interaction between *Campylobacter* and PPI? Alternatively, was it a PPI-IBS effect that was observed regardless of the prior infection with *Campylobacter*?

Other interesting avenues

If the linkage of SGSS data becomes available, it might be possible to improve the ascertainment of diagnosis date by selecting both patients with a Read code indicative of GI illness and those specific for the aetiology. The consultations and tests record in the month before and after their date of entry into the cohort can be compared. If a peak is observed in either consultations or tests before entry, this may be indicative of the diagnosis date provided they have a confirmed laboratory diagnosis in SGSS.

The SGSS-linked CPRD data can also be used to address current laboratory testing and reporting patterns in CPRD. Laboratory testing and recording of results was variable amongst patients in the cohort. Some of the patients also did not have a laboratory test record but had a Read code for *Campylobacter* or NTS. A qualitative study was conducted to understand if GPs follow existing guidelines when requesting a laboratory test for GI infection. The study found that not all adhered

the guidelines [165]. Tests results are more likely to be recorded if there is a value. Hence, they are not missing not at random [181]. Microbiological tests such as stool culture for GI infection are usually reported as presence or absence of a pathogen, hence they may be recorded within the free text option (CPRD data specification). A quantitative study to determine if requests differ by region or practice assessed against the guidelines for testing may elucidate why some patients have a specific Read code for GI infection while others only have Read codes indicative of GI infection.

8.6 Reflections on DPhil

Preparing this thesis has allowed me to reflect on my personal learning. I have gained an incredible amount of knowledge and skills during my studies. Practically, I have developed and improved my data management skills using advanced programming methods in STATA, learned to conduct analyses which were new to me, such as meta-analysis of proportions and health economic assessments. I have also gained a better theoretical understanding of the challenges of handling, analysing and interpreting linked routinely-collected electronic health records, and introductory concepts in economic evaluation. These were applied while developing the study design and analysis plan for each of the empirical studies.

It is indeed a testament of the journey of a thousand miles beginning with one step. The journey was not without its fair share of turns, twists and steep mountain climbs, some of which were beyond me. I did not receive the CPRD-HES linked data until I was six terms into the course of studies, while the SGSS-HES linked data was not available until my eighth term. Although these third-party dependencies significantly impacted the study commencement, with the benefit of hindsight, I should have sought approval for a pilot study (budget permitting) from the onset to develop the algorithm for case definition, selection, and a conceptual framework to address potential confounding. This would have made my course of studies more efficient.

Notwithstanding, the Read codes for case selection, exposures, outcomes, and covariates, which were all time-consuming to identify and classify is now a resource available to other researchers.

Additionally, there was no departmental wide information governance (IG) toolkit in place when I commenced my study. The IG toolkit is a series of policies to ensure adherence to information security when using NHS data. With the assistance of my supervisors, I put one in place for this project. This has now formed the backbone of the departmental wide IG policies.

I am grateful for my funding to complete this DPhil by the NIHR Health Protection Research Unit in Gastrointestinal Infections. Attending the annual scientific meeting of the unit, provided a platform to share my work with a multidisciplinary audience from molecular microbiologists characterising the gut microbiome; using whole genome sequencing to detect outbreaks and redefine what constitutes an outbreak to social scientists seeking to unravel the socioeconomic differences in the risks and consequences of gastrointestinal infections. Findings from this thesis (systematic review has been published and other manuscripts in preparation), as well as different outputs from the unit, are all extending the understanding of the burden of infections in the UK.

8.7 Conclusion

The key implication for this thesis is the need to improve control strategies in the prevention of *Campylobacter* and NTS infections. This is warranted as patients develop sequelae, which significantly impacts the NHS and places an additional burden on scarce resources. Clinicians should be aware of the elevated risk of post-infectious IBS amongst those prescribed PPI. There is a need to establish if a dose-response relationship exists between PPI usage amongst patients with *Campylobacter* infection and the onset of sequelae. If this is observed, further guidance can be provided to clinicians prescribing PPI.

It is crucial that the general public are aware of the sequelae of *Campylobacter* and NTS infections as an additional negative consequence of these GI infections. These will further strengthen public

health prevention campaigns. Policy makers need to ensure an equitable national health service for all patients who access primary care as the needs of those who use the services infrequently may be masked by heavy users such as older people and those with existing comorbidities.

Future initiatives to understand the burden of GI infections can incorporate the estimates of sequelae and associated costs from this thesis to produce the DALY metric specifically designed for zoonotic infections. This will improve the understanding of the societal burden of zoonotic infections such as *Campylobacter* and NTS and allow international comparisons to inform prevention strategies. Further, the methods in this thesis can be replicated for other acute infections commonly diagnosed within primary care settings.

Should linked laboratory, primary care and hospital data become available, it would provide a clearer temporal relationship between onset of GI infection and sequelae. Additionally, whole genome sequencing will further elucidate the host-pathogen relationship in the onset of sequelae and predisposing factors.

8.8 References

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APPENDICES

Appendix 3-1 Searches

Pubmed

Search	Query	Items found
#25	Search ((((("Campylobacter Infections"[Mesh]) OR "Salmonella Infections"[Mesh]) OR ((campylobacter*[Title/Abstract]) OR salmonella*[Title/Abstract]))) AND (((((((#9) OR "Guillain-Barre Syndrome"[Mesh]) OR "Inflammatory Bowel Diseases"[Mesh]) OR "Irritable Bowel Syndrome"[Mesh]) OR "Arthritis, Reactive"[Mesh]) OR "Hemolytic-Uremic Syndrome"[Mesh]) OR (Sequel* OR Complication* OR Long-term OR Longterm OR chronic OR Guillain* OR HUS OR "Haemolytic uremic syndrome" OR "Hemolytic uremic syndrome" OR "Hemorrhagic uremic syndrome" OR "Haemorrhagic uraemic syndrome" OR Reiter* OR Arthritis* OR "Irritable bowel syndrome" OR IBS OR "inflammatory bowel disease" OR colitis OR crohn*)) Filters: Publication date from 2011/01/01 to 2016/12/31	1536
#24	Search ((((("Campylobacter Infections"[Mesh]) OR "Salmonella Infections"[Mesh]) OR ((campylobacter*[Title/Abstract]) OR salmonella*[Title/Abstract]))) AND (((((((#9) OR "Guillain-Barre Syndrome"[Mesh]) OR "Inflammatory Bowel Diseases"[Mesh]) OR "Irritable Bowel Syndrome"[Mesh]) OR "Arthritis, Reactive"[Mesh]) OR "Hemolytic-Uremic Syndrome"[Mesh]) OR (Sequel* OR Complication* OR Long-term OR Longterm OR chronic OR Guillain* OR HUS OR "Haemolytic uremic syndrome" OR "Hemolytic uremic syndrome" OR "Hemorrhagic uremic syndrome" OR "Haemorrhagic uraemic syndrome" OR Reiter* OR Arthritis* OR "Irritable bowel syndrome" OR IBS OR "inflammatory bowel disease" OR colitis OR crohn*))	11047
#23	Search ((((((#9) OR "Guillain-Barre Syndrome"[Mesh]) OR "Inflammatory Bowel Diseases"[Mesh]) OR "Irritable Bowel Syndrome"[Mesh]) OR "Arthritis, Reactive"[Mesh]) OR "Hemolytic-Uremic Syndrome"[Mesh]) OR (Sequel* OR Complication* OR Long-term OR Longterm OR chronic OR Guillain* OR HUS OR "Haemolytic uremic syndrome" OR "Hemolytic uremic syndrome" OR "Hemorrhagic uremic syndrome" OR "Haemorrhagic uraemic syndrome" OR Reiter* OR Arthritis* OR "Irritable bowel syndrome" OR IBS OR "inflammatory bowel disease" OR colitis OR crohn*)	4189495

Search	Query	Items found
#22	Search Sequel* OR Complication* OR Long-term OR Longterm OR chronic OR Guillain* OR HUS OR "Haemolytic uremic syndrome" OR "Hemolytic uremic syndrome" OR "Hemorrhagic uremic syndrome" OR "Haemorrhagic uraemic syndrome" OR Reiter* OR Arthritis* OR "Irritable bowel syndrome" OR IBS OR "inflammatory bowel disease" OR colitis OR crohn*	4079420
#20	Search "Hemolytic-Uremic Syndrome"[Mesh]	4978
#18	Search "Arthritis, Reactive"[Mesh]	3802
#16	Search "Irritable Bowel Syndrome"[Mesh]	5141
#14	Search "Inflammatory Bowel Diseases"[Mesh]	65279
#12	Search "Guillain-Barre Syndrome"[Mesh]	3892
#9	Search "complications" [Subheading] Schema: syn	1825334
#7	Search (("Campylobacter Infections"[Mesh]) OR "Salmonella Infections"[Mesh]) OR ((campylobacter*[Title/Abstract]) OR salmonella*[Title/Abstract])	90649
#6	Search (campylobacter*[Title/Abstract]) OR salmonella*[Title/Abstract]	77934
#5	Search "Salmonella Infections"[Mesh]	32354
#2	Search "Campylobacter Infections"[Mesh]	6381

Embase

# ▲	Searches	Results
1	(salmonella* or campylobacter*).ti,ab.	82925
2	exp salmonellosis/	27049
3	campylobacteriosis/	1205
4	1 or 2 or 3	97594
5	exp inflammatory bowel disease/	105586
6	Guillain Barre syndrome/	11626
7	irritable colon/	18690
8	reactive arthritis/	2922
9	hemolytic uremic syndrome/	8993
10	(Sequel* or Complication* or Long-term or Longterm or chronic or Guillain* or HUS or Haemolytic uremic syndrome or Hemolytic uremic syndrome or Hemorrhagic uremic syndrome or Haemorrhagic uraemic syndrome or Reiter* or Arthritis* or Irritable bowel syndrome or IBS or inflammatory bowel disease or colitis or crohn*).ti,ab.	3044735
11	5 or 6 or 7 or 8 or 9 or 10	3073733
12	4 and 11	7690
13	limit 12 to yr="2011 -Current"	2132

CAB Abstracts

# ▲	Searches	Results
1	(salmonella* or campylobacter*).ti,ab.	33356
2	salmonella/ or salmonellosis/	30603
3	exp campylobacter/	6653
4	salmonella.od.	18096
5	campylobacter*.od.	6626
6	1 or 2 or 3 or 4 or 5	37086
7	exp inflammatory bowel diseases/	2975
8	irritable colon.sh.	1300
9	arthritis.sh.	4077
10	Guillain-Barre syndrome.sh.	138
11	haemolytic uraemic syndrome.sh.	298
12	(Sequel* or Complication* or Long-term or Longterm or chronic or Guillain* or HUS or Haemolytic uremic syndrome or Hemolytic uremic syndrome or Hemorrhagic uremic syndrome or Haemorrhagic uraemic syndrome or Reiter* or Arthritis* or Irritable bowel syndrome or IBS or inflammatory bowel disease or colitis or crohn*).ti,ab.	221963
13	7 or 8 or 9 or 10 or 11 or 12	222937
14	6 and 13	1032
15	limit 14 to yr="2011 -Current"	433

Agricola

Query	Results
(salmonella OR campylobacter) AND (guillain OR arthritis OR "inflammatory bowel" OR "irritable bowel" OR colitis OR crohns)	32
(salmonella OR campylobacter) AND (sequelae OR Complication OR complications OR long-term OR longterm OR chronic)	0
(salmonella OR campylobacter) AND "uremic syndrome"	0

Search summary

Database	Interface	Coverage	Dates	Hits	After duplicates
AGRICOLA	http://agricola.nal.usda.gov/		29.04/2016	32	32
CAB abstracts	OvidSP	2000 to 2016 Week 15	28/04/2016	433	182
Embase	OvidSP	1974 to 2016 April 27	28/04/2016	2132	1036
PubMed	http://www.pubmed.gov		28/04/2016	1536	1536
Total:				**4133**	**2786**
Animal & plant studies excluded				**363**	
Duplicates:				1347	
Final total:				**2422**	

Appendix 3-2 Data extraction tool

Variable	Description
Entry ID	Unique ID for each entry on the data extraction form. First available Id is "1002" and automatically generated for the rest.
Article ID	Reference ID, See Article ID Worksheet for the list.
Author	Last name of the first author.
Year of publication	Year article published
Country	Country from which study population is taken
Study design	The study design used to gather information pertaining to the pathogen and chronic sequelae of interest. Options are: - Retrospective outbreak*: used historic outbreak and historic disease status records. - Prospective outbreak*: cases of pathogen identified from the current or recent outbreak and followed forward in time to determine chronic sequelae status. - Retrospective population surveillance: historic cases of pathogen and disease identified from population surveillance and connected. - Prospective population surveillance: the case of pathogen identified from population surveillance, followed forward in time to determine disease status. - Cohort: study begins before illness from pathogen occurs. Cases and controls are identified and both are followed forward in time to determine pathogen exposure and associated sequelae status. - Case control: cases of the pathogen are identified, matched with controls and followed forward to time to determine disease status. - Cross sectional: looks at the population at a point in time. Not linked to outbreak or population surveillance data. - Other - Unknown **Note: some studies will use a case control study to determine the source/risk factors of the outbreak. This would* ***NOT*** *be classified as a case control study as it does not pertain to the data on the pathogen/sequelae relationship.*

Variable	Description
Source of data	What type of data source was used to gather the information used in the analysis. Options are: - outbreak in hospital - outbreak in community - hospitalized cases - surveillance of population (sporadic or outbreak) – this is meant to imply that ongoing population surveillance will often capture both sporadic and outbreak cases. - disease registry - notifiable diseases - sporadic cases - unknown - other
Outbreak source	For outbreak data, indicate the source of the outbreak. Options are: - food - meat - food - vegetable - food- other - food - dairy - waterborne - direct animal contact (e.g. farm/zoo/pets) - daycare/nursery - unknown Otherwise enter NA (not applicable)
Date for data collection	Year (or range of years) data was collected. If not specifically reported enter "pre-publication date" (e.g. Pre-1994). Do not need to include days/months. If multiple years were included, separate with a comma (2004, 2010) unless data collection occurred over the entire period; indicate a range with a hyphen (2004-2010).
Season	Indicate season applicable to the range for data collection. Definitions: Fall – September, October, November Winter – December, January, February Spring – March, April, May Summer –June, July, August The overlap between seasons (e.g. fall/winter) and yearlong are acceptable. For data collection that captures more than one year enter "various".
Age range/categories	Age range (in years) used for the population with pathogen/sequelae of interest. No median age needed. Report category (e.g. Adults over 18) only if no range is given.
Gender	Indicate the gender mix of the population by reporting the number or (proportion if number not available) of participants who were female ("Gender F") and who were

Variable	Description
	male ("Gender M"). If information is not reported enter NR in each column.
Pathogen	Enter pathogen name. If there are multiple pathogens per study, create new rows following the first for each pathogen/sequelae combination. You will need to repeat the Article ID and Author in these cases. Options: - E. coli - Campylobacter - Salmonella
Diagnostic Test Used (Pathogen)	Specify the type of test used to diagnose the pathogen. The options are: - Laboratory confirmed - Probable cases based on case definition from the study (for example Walkerton Health Study) - Other - Not reported Classify on the level most appropriate to outcome analysis. Create new rows to report pathogen diagnosis for different outcomes. *For example: if the study reports the number of cases of HUS associated with all "probable cases based on case definition from study" (e.g: 10 out of 300 probable cases – outcome 1 (10/300), row 1) as well as the number of cases of HUS associated with culture confirmed cases (of the 10 HUS overall, 9 were patients who were culture confirmed out of a total of 150 culture confirmed cases – outcome 2(9/150), row 2) this would be two separate rows with two separate pathogen diagnosis and outcomes for the same study. Can only do this when the paper SPECIFICALLY says that the chronic sequelae cases were also lab confirmed.*
Pathogen Subtype	Enter species name or serotype (salmonella) (NOT CAPITALIZED) (E.g.: jejuni NOT Jejuni). Enter NR (not reported) if it's not specified. Create new rows for each species/serotype given ONLY IF outcome information is available at the species/serotype level. *For example: A study looked at campylobacter and differentiated between C. jejuni and C. fetus and reported outcomes for both; The number of people positive for campylobacter jejuni who developed IBS was 1/100 (outcome 1, row 1), the number of people positive for campylobacter fetus who developed IBS was 0/130 (outcome 2, row 2). The total number of people with campylobacter who developed IBS was 1/230 (outcome 3, row 3).*
Fever	Record the number or proportion reported in the study
Vomiting	Record the number or proportion reported in the study

Variable	Description
Diarrhoea	Record the number or proportion reported in the study
Bloody Diarrhoea	Record the number or proportion reported in the study
Abdominal pain	Record the number or proportion reported in the study
GP Visit/Physician	Record the number or proportion reported in the study
A&E/emergency Department	Record the number or proportion reported in the study
Hospitalised	Record the number or proportion reported in the study
Antibiotic Reported	Options: - Yes - No
Antibiotics Numbers	Record the number or proportion reported in the study. If the name of the antibiotics is given indicate this. E.g (Azithromycin – 3/10)
Other drugs	Record the number or proportion reported in the study. If the name of the drug is given indicate this. E.g. (Zantac – 3/10)
Underlying condition reported	Options -Yes -No
Underlying condition notes	Record the name of the condition and the number of people/proportion. E.g. cancer -3/10
Complication	Specify which sequelae the study reports on as an outcome. If there are multiple sequelae per study, create new rows for each pathogen/sequelae combination. You will need to manually enter the ArticleID and author in these cases. Sequelae of interest are: - HUS (Haemolytic Anaemia, Thrombocytopenia) - Renal Failure/Decreased Renal Function - Reactive Arthritis (ReA) - Reiters - Combined ReA/Reiters - Irritable Bowel Syndrome - Post Infectious Irritable Bowel Syndrome (PI-IBS) - Crohn's Disease - Ulcerative Colitis - Inflammatory Bowel Disease - Guillain Barré (Acute idiopathic polyneuritis/Infectious polyneuritis - Acute inflammatory polyneuropathy; Acute inflammatory demyelinating polyneuropathy)

Variable	Description
	- Miller-Fisher Syndrome
Diagnosis (Sequelae)	Specify how the diagnosis for the sequelae was performed. Options include: - Self reported disease status (E.g. Participant says they have ReA) - Self reported based on a validated scale (E.g. Used Questionnaire Utilizing Epidemic Spondyloarthropathy Traits 2 (QUEST2) survey for ReA diagnosis) - Disease status confirmed by a specialist (diagnosis of ReA confirmed by Rheumatologist) - Other trained health professional (diagnosis performed by trained health professionals. E.g. Nurses trained for a research project) - Not reported - Combination (If more than one method was used, stated methods used in the comments section)
Follow up	Time from Illness from Pathogen to Evaluation for complication. Enter the maximum length of time (in days) between the onset of illness and evaluation for the chronic sequelae. Enter NR if not reported.
Number of people with the pathogen (denominator)	Number of people with the pathogen who are used for the analysis for the outcome of interest.
Number of people with sequelae (numerator)	Number of people with the pathogen who went on to develop the chronic sequelae of interest
Funding Source	Record what is reported, if blank, Enter NR
Conflicts of interest	Record what is reported, if blank, Enter NR
Comments	Insert any comments regarding the study design, symptoms or outcome

Appendix 3-3 Proportion developing complications following *Campylobacter* infection

Author & Year	Pathogen Subtype	Pathogen_Diagnosis	Complication	Diagnosis_ Complication	Definition of Complication	Follow-up	No. with pathogen	No. with complication	Proportion
Guillain Barré Syndrome									
Baker 2012[19]	N.R	Laboratory Confirmed	N.R	Specialist	Yes - Validated Criteria	60	8448	34	0.40%
Doorduyn 2008[57]	N.R	Laboratory Confirmed	N.R	Self-reported disease status	N.R	1080	434	0	0.00%
Gardner 2011[73]	*C. jejuni*	Laboratory Confirmed	No	Specialist	N.R	9	45	1	2.22%
Helms 2006[56]	N.R	Laboratory Confirmed Probable	No	Physician/Medical records	N.R	365	17991	6	0.03%
McCarthy 1999[69]	N.R		No	Physician/Medical records	Yes - Author's Definition	180	8086	0	0.0%
McCarthy 2001[70]	*C. jejuni*	Laboratory Confirmed	No	Physician/Medical records	Yes - Validated Criteria	180	29563	9	0.03%
Tam 2006[71]	N.R	Laboratory Confirmed	No	Physician/Medical records	Yes - Validated Criteria	60	15587	3	0.02%
Wang 2008[72]	*C. coli*	Laboratory Confirmed	No	Physician/Medical records	N.R	N.R	24	0	0.00%
Wang 2008[72]	*C. jejuni*	Laboratory Confirmed	No	Physician/Medical records	N.R	N.R	80	0	0.00%
Wang 2008[72]*	*C. jejuni/coli*	Laboratory Confirmed	No	Physician/Medical records	N.R	N.R	104	0	0.00%
Irritable bowel syndrome									
Dunlop 2003[63]	*C. coli/jejuni*	Laboratory Confirmed	No	Self-reported based on validated scale	Yes - Validated Criteria	90	747	103	13.79%
Helms 2006[56]	N.R	Laboratory Confirmed	No	Physician/Medical records	N.R	365	17991	161	0.89%

Author & Year	Pathogen Subtype	Pathogen_Diagnosis	Complication	Diagnosis_ Complication	Definition of Complication	Follow-up	No. with pathogen	No. with complication	Proportion
Moss-Morris 2006[64]	N.R	Laboratory Confirmed	No	Self-reported based on validated scale	N.R	90	553	83	15.01%
Moss-Morris 2006[64]	N.R	Laboratory Confirmed	No	Self-reported based on validated scale	N.R	180	536	59	11.01%
PorterB 2013[22]	N.R	Laboratory Confirmed	No	Physician/Medical records	Yes - Validated Criteria	N.R	738	37	5.01%
Saps 2008[68]	N.R	Laboratory Confirmed	N.R	Self-reported based on validated scale	Yes -Validated Criteria	180	6	1	16.67%
Spence 2007[65]	*C. jejuni*	Laboratory Confirmed	No	Self-reported based on validated scale	N.R	180	620	49	7.90%
Spiller 2000[61]	*C. jejuni*	Laboratory Confirmed	N.R	Self-reported based on validated scale	N.R	365	31	4	12.90%
Ternhag 2008[59]	*C. coli/jejuni*	Laboratory Confirmed	NR	Physician/Medical records	N.R	365	57425	15	0.03%
Thornley 2001[62]	N.R	Laboratory Confirmed	No	Self-reported based on validated scale	N.R	180	188	17	9.04%
Reactive arthritis									
Bremell 1991[32]	*C. jejuni*	Laboratory Confirmed	N.R	Self-reported disease status	Yes - Author's Definition	30	66	1	1.52%
Doorduyn 2008[57]	N.R	Laboratory Confirmed	N.R	Self-reported disease status	N.R	1080	434	20	4.61%
EastmondA1983[74]	N.R	Laboratory Confirmed	No	Physician/Medical records	N.R	90	88	1	1.14%
Gumpel 1981[24]	N.R	Laboratory Confirmed	N.R	Physician/Medical records	N.R	N.R	77	8	10.39%
HannuA 2002[33]*	*C. coli/jejuni/undetermined*	Laboratory Confirmed	No	Specialist	Yes - Author's Definition	60	609	45	7.39%
HannuA 2002[33]	*C. coli/jejuni/undetermined*	Laboratory Confirmed	No	Self-reported disease status	Yes - Author's Definition	60	609	7	1.15%

Author & Year	Pathogen Subtype	Pathogen_Diagnosis	Complication	Diagnosis_ Complication	Definition of Complication	Follow-up	No. with pathogen	No. with complication	Proportion
HannuA 2002[33]	*C. jejuni*	Laboratory Confirmed	No	Specialist	Yes - Author's Definition	60	535	37	6.92%
HannuA 2002[33]	*C. coli*	Laboratory Confirmed	No	Specialist	Yes - Author's Definition	60	61	8	13.11%
HannuA 2002[33]	Undetermined	Laboratory Confirmed	No	Specialist	Yes - Author's Definition	60	13	0	0.00%
Helms 2006[56]	N.R	Laboratory Confirmed	No	Physician/Medical records	N.R	365	17991	22	0.12%
Kosunen 1981[25]	*C. jejuni*	Laboratory Confirmed	N.R	Not reported	N.R	365	342	8	2.34%
LochtA 2002[34]	*C. coli/jejuni*	Laboratory Confirmed	No	Self-reported disease status	Yes - Author's Definition	28	173	27	15.61%
Petersen 1996[55]	*C. coli/jejuni*	Laboratory Confirmed	N.R	Physician/Medical records	N.R	N.R	41	0	0.00%
Pitkanen 1983[29]	*C. jejuni*	Laboratory Confirmed		Combination	N.R	N.R	188	9	4.79%
Pitkanen 1981[26]	*C. jejuni*	Laboratory Confirmed	N.R	Combination	N.R	N.R	56	4	7.14%
Ponka 1984[30]	*C. jejuni*	Laboratory Confirmed	N.R	Self-reported disease status	N.R	N.R	383	6	1.57%
Schiellerup 2008[75]	N.R	Laboratory Confirmed	No	Self-reported based on validated scale	Yes -Validated Criteria	28	1003	131	13.06%
Schoenberg-Norio 2010[76]	*C. jejuni*	Laboratory Confirmed	No	Physician/Medical records	Yes - Author's Definition	60	201	8	3.98%
Short 1982[27]	*C. jejuni*	Laboratory Confirmed	N.R	Physician/Medical records	N.R	42	15	0	0.00%
Ternhag 2008[59]*	*C.coli/jejuni*	Laboratory Confirmed	N.R	Physician/Medical records	N.R	365	57425	15	0.03%
Ternhag 2008[59]	*C.coli/jejuni*	Laboratory Confirmed	N.R	Physician/Medical records	N.R	90	57425	13	0.02%
Townes 2008[60]	N.R	Laboratory Confirmed	No	Physician/Medical records	Yes - Author's Definition	56	2384	33	1.38%

Author & Year	Pathogen Subtype	Pathogen_Diagnosis	Complication	Diagnosis_ Complication	Definition of Complication	Follow-up	No. with pathogen	No. with complication	Proportion
Uotila 2014[20]	N.R	Laboratory Confirmed	No	Self-reported disease status	Yes - Author's definition	630	73	42	57.53%
Reiters syndrome									
Doorduyn 2008[57]	N.R	Laboratory Confirmed	No	Self-reported disease status	N.R	1080	434	0	0.00%
PorterA 2013[21]	N.R	Laboratory Confirmed	No	Physician/Medical records	Yes - Validated Criteria	180	738	1	0.14%

Yes - Validated Criteria‡ - These include ICD-9/ICD-10 definition, validated questionnaire definition such as Rome I, Rome II, Rome III criteria for IBS

Appendix 3-4 Proportion developing complications following NTS infection

Author & Year	Pathogen Serotype†	Pathogen_Diagnosis	Complication	Diagnosis_ Complication	Definition of Complication‡	Follow-up	No. with pathogen	No. with complication	Proportion
Irritable bowel syndrome									
Helms 2006[56]*	Multiple	Laboratory Confirmed	No	Physician/Medical records	N.R	365	27894	252	0.90%
Helms 2006[56]	Enteritidis	Laboratory Confirmed	No	Physician/Medical records	N.R	365	14533	125	0.86%
Helms 2006[56]	Typhimurium	Laboratory Confirmed	No	Physician/Medical records	N.R	365	7021	67	0.95%
Helms 2006[56]	Other NTS	Laboratory Confirmed	No	Physician/Medical records	N.R	365	6034	60	0.99%
McKendrick 1994[66]	Enteritidis PT4	Probable	No	Self-reported based on validated scale	Yes - Validated Criteria	365	38	12	31.58%
Mearin 2005[67]	Enteritidis	Probable	N.R	Self-reported based on validated scale	Yes - Validated Criteria	365	266	31	11.65%
PorterB 2013[22]	N.R	Laboratory Confirmed	No	Physician/Medical records	Yes - Validated Criteria	NR	624	32	5.13%
Saps 2008[68]	N.R	Laboratory Confirmed	N.R	Self-reported based on validated scale	Yes -Validated Criteria	180	24	9	37.50%

Author & Year	Pathogen Serotype†	Pathogen_Diagnosis	Complication	Diagnosis_ Complication	Definition of Complication‡	Follow-up	No. with pathogen	No. with complication	Proportion
Ternhag 2008[59]	Multiple	Laboratory Confirmed	N.R	Physician/Medical records	N.R	365	34664	5	0.01%
Urfer 2000[46]	Braenderup	Laboratory Confirmed	N.R	Self-reported	N.R	180	127	12	9.45%
Reactive arthritis									
Arnedo-Pena 2010[54]	Hadar	Probable	No	Self-reported based on validated scale	Yes - Author's Definition	90	155	16	10.32%
Arnedo-Pena* 2010[54]	Hadar PT2	Laboratory Confirmed	No	Specialist	Yes - Author's Definition	90	67	6	8.96%
Arnedo-Pena 2010[54]	Hadar	Probable	No	Specialist	Yes - Author's Definition	90	155	13	8.39%
Buxton 2002[49]	Typhimurium	Laboratory Confirmed	No	Self-reported based on validated scale	Yes - Validated Criteria	120	66	17	25.76%
Buxton 2002[49]	Typhimurium	Laboratory Confirmed	No	Specialist	Yes - Author's Definition	90	61	4	6.56%
Doorduyn 2008[57]	N.R	Laboratory Confirmed	Yes	Self-reported	N.R	1080	181	8	4.42%
Dworkin 2001	Enteritidis	Probable	N.R	Self-reported	Yes - Author's definition	30	217	63	29.03%
EastmondB1983[37]	N.R	Laboratory Confirmed	N.R	Physician/Medical records	Yes - Author's definition	60	418	8	1.91%

Author & Year	Pathogen Serotype†	Pathogen_Diagnosis	Complication	Diagnosis_ Complication	Definition of Complication‡	Follow-up	No. with pathogen	No. with complication	Proportion
Ekman 2000[44]*		Laboratory Confirmed	No	Specialist			198	8	4.04%
Ekman 2000[44]	N.R	Laboratory Confirmed	No	Self-reported	N.R	N.R	198	13	6.57%
	N.R Typhimurium	Laboratory Confirmed			N.R	N.R	330	13	3.94%
Hakansson 1976[36]			N.R	N.R	N.R	N.R			
HannuB 2002[50]	Typhimurium DT 193	Laboratory Confirmed	No	Specialist	Yes - Author's definition	60	63	5	7.94%
Helms 2006[56]*	Multiple	Laboratory Confirmed	No	Physician/Medical records	N.R	365	27894	87	0.31%
Helms 2006[56]	Enteritidis	Laboratory Confirmed	No	Physician/Medical records	N.R	365	14533	50	0.34%
Helms 2006[56]	Typhimurium	Laboratory Confirmed	No	Physician/Medical records	N.R	365	7021	24	0.34%
Helms 2006[56]	other NTS	Laboratory Confirmed	No	Physician/Medical records	N.R	365	6034	13	0.22%
Lee 2005[52]*	Typhimurium PT 135a	Laboratory Confirmed	No	Physician/Medical records	Yes - Author's definition	90	261	38	14.56% - All
Lee 2005[52]	Typhimurium PT 135a	Laboratory Confirmed	No	Physician/Medical records	Yes - Author's definition	90	54	13	24.07% - Children

Author & Year	Pathogen Serotype†	Pathogen_Diagnosis	Complication	Diagnosis_ Complication	Definition of Complication‡	Follow-up	No. with pathogen	No. with complication	Proportion
Lee 2005[52]	Typhimurium PT 135a	Laboratory Confirmed	No	Physician/Medical records	Yes - Author's definition	90	207	25	12.08% - Adults
Locht 1993[39]	Enteritidis	Probable	N.R	Self-reported	Yes - Author's Definition	28	108	17	15.74%
Locht 1993[39]*	Enteritidis	Laboratory Confirmed	N.R	Self-reported	Yes - Author's Definition	28	89	16	17.98%
LochtB 2002[51]	N.R	Probable	No	Self-reported	Yes - Author's definition	28	91	17	18.68%
Mattila 1994[40]	Monophasic	Laboratory Confirmed	N.R	Specialist	Yes - Author's definition	150	246	16	6.50%
Mattila 1998[43]	Bovismorbificans	Laboratory Confirmed	No	Specialist	Yes - Author's definition	90	191	22	11.52%
McColl 2000[45]*	Tyhimurium	Probable	N.R	Self-reported	Yes - Author's definition	90	312	13	4.17%
McColl 2000[45]	Tyhimurium PT9	Probable	N.R	Self-reported	Yes - Author's definition	90	112	6	5.36%
Petersen 1996[55]	Multiple	Laboratory Confirmed	N.R	Physician/Medical records	N.R	N.R	127	7	5.51%
Petersen 1996[55]	Tyhimurium	Laboratory Confirmed	N.R	Physician/Medical records	N.R	N.R	40	3	7.50%
Petersen 1996[55]	Enteritidis	Laboratory Confirmed	N.R	Physician/Medical records	N.R	N.R	48	4	8.33%

Author & Year	Pathogen Serotype†	Pathogen_Diagnosis	Complication	Diagnosis_ Complication	Definition of Complication‡	Follow-up	No. with pathogen	No. with complication	Proportion
Petersen 1996[55]	Other NTS	Laboratory Confirmed	N.R	Physician/Medical records	N.R	N.R	39	0	0.00%
Rohekar 2008[53]	Enteritidis PT 13	Laboratory Confirmed	N.R	Self-reported	Yes - Validated Criteria	N.R	104	65	62.50%
Rudwaleit 2001[48]	Enteritidis	Laboratory Confirmed	No	Physician/Medical records	N.R	120	286	0	0.00%
Samuel 1995[42]	N.R	Probable	N.R	Physician/Medical records	N.R	112	321	23	7.17%
Schiellerup 2008[75]*	N.R	Laboratory Confirmed	No	Self-reported based on validated scale	Yes -Validated Criteria	28	619	104	16.80%
Schiellerup 2008[75]	Multiple Typhimurium	Laboratory Confirmed	No	Self-reported based on validated scale	Yes -Validated Criteria	28	193	29	15.03%
Schiellerup 2008[75]	Enteritidis	Laboratory Confirmed	No	Self-reported based on validated scale	Yes -Validated Criteria	28	270	49	18.15%
Schiellerup 2008[75]	Other NTS	Laboratory Confirmed	No	Self-reported based on validated scale	Yes -Validated Criteria	28	156	26	16.67%
Ternhag 2008[59]	Multiple	Laboratory Confirmed	N.R	Physician/Medical records	N.R	365	34664	27	0.08%

Author & Year	Pathogen Serotype†	Pathogen_Diagnosis	Complication	Diagnosis_ Complication	Definition of Complication‡	Follow-up	No. with pathogen	No. with complication	Proportion
Thomson 1994[41]	Enteritidis	Probable	No	Physician/Medical records	Yes - Author's Definition	60	29	8	27.59%
Thomson 1992[38]	Multiple	Probable	No	Self-reported	Yes - Author's definition	28	73	6	8.22%
Townes 2008[60]	N.R	Laboratory Confirmed	No	Physician/Medical records	N.R	56	1356	17	1.25%
Tuompo 2013[23]	Multiple	Laboratory Confirmed	No	Combination	Yes - Author's definition	540	496	22	4.44%
Urfer 2000[46]	Braedenrup	Laboratory Confirmed	N.R	Self-reported	N.R	180	127	1	0.79%
Reiters syndrome									
Doorduyn 2008[57]	N.R	Laboratory Confirmed	Yes	Self-reported	N.R	1080	193	0	0.00%
Dworkin 2001[47]	Enteritidis	Probable	N.R	Self-reported	Yes - Author's definition	30	217	6	2.76%
Mattila 1998[43]	Bovismorbificans	Laboratory Confirmed	No	Specialist	Yes - Author's definition	90	191	0	0.00%
PorterA 2013[21]	N.R	Laboratory Confirmed	No	Physician/Medical records	Yes - Validated Criteria	180	624	3	0.48%
Thomson 1994[41]	Enteritidis	Probable	No	Physician/Medical records	Yes - Author's Definition	60	29	2	6.90%

Author Year* - Outcome measures used for forest plots; Multiple† - Enteritidis, Typhimurium & Other NTS serotypes; Yes - Validated Criteria‡ - These include ICD-9/ICD-10 definition, validated questionnaire definition such as Rome I, Rome II, Rome III criteria for IBS and QUEST2 - Questionnaire Utilizing Epidemic Spondyloarthropathy traits for reactive arthrit

Appendix 4-1 – Ethics and legal approvals

Appendix 4-1-1 NHS Research Ethics Committee Approval

NHS
Health Research Authority
NRES Committee Yorkshire & The Humber - South Yorkshire
Unit 001
Jarrow Business Centre
Rolling Mill Road
Jarrow
Tyne and Wear
NE32 3DT

Telephone: 0191 428 3561

12 August 2015

Ms. Oluwaseun Esan
Department of Primary Care Health Sciences
New Radcliffe House
Observatory Street
Oxford
OX2 6GG

Dear Ms. Esan

Study title:	**Retrospective cohort study to estimate the burden of complications from common gastrointestinal infections and remediable factors that contribute to this burden.**
REC reference:	**15/YH/0395**
Protocol number:	**PID11494**
IRAS project ID:	**177765**

The Proportionate Review Sub-committee of the NRES Committee Yorkshire & The Humber - South Yorkshire reviewed the above application on 12 August 2015.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Assistant Miss Kerry Dunbar, nrescommittee.yorkandhumber-southyorks@nhs.net Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Appendix 4-1-2 HRA Confidential Advisory Committee Approval

NHS
Health Research Authority

Skipton House
80 London Road
London
SE1 6LH

03 November 2016

Ms. Oluwaseun Esan
Department of Primary Care Health Sciences
New Radcliffe House
Observatory Street, Oxford
OX2 6GG
oluwaseun.esan@phc.ox.ac.uk

Dear Ms Esan

Application title:	**Estimating the burden of complications of gastrointestinal infections**
CAG reference:	**16/CAG/0027**
IRAS project ID:	**177765/910552/4/864**
REC reference:	**15/YH/0395**

Thank you for your research application, submitted for approval under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 to process patient identifiable information without consent. Approved applications enable the data controller to provide specified information to the applicant for the purposes of the relevant activity, without being in breach of the common law duty of confidentiality, although other relevant legislative provisions will still be applicable.

The role of the Confidentiality Advisory Group (CAG) is to review applications submitted under these Regulations and to provide advice to the Health Research Authority on whether an application should be approved, and if so, any relevant conditions. This application was considered at the CAG meeting held on 12 February 2016.

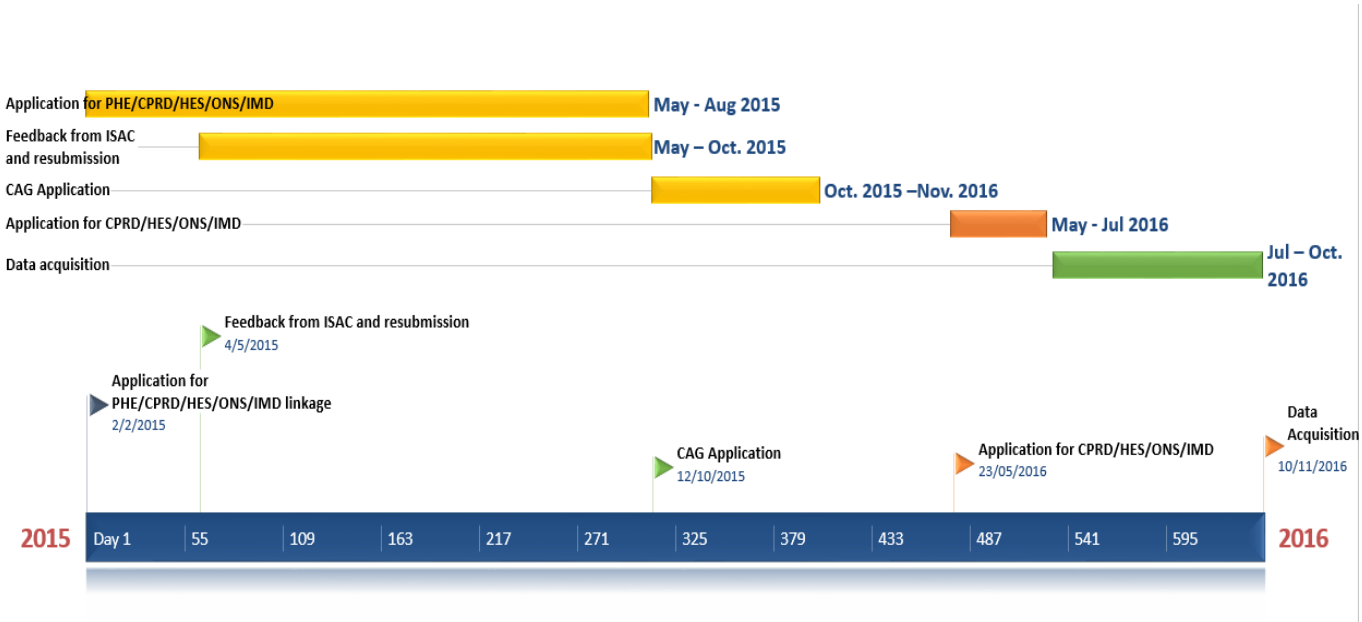
Health Research Authority approval decision

The Health Research Authority, having considered the advice from the Confidentiality Advisory Group as set out below, has determined the following:

1. The application is approved, subject to compliance with the standard and specific conditions of approval.

This letter should be read in conjunction with the outcome letter dated 4 March 2016.

Appendix 4-2 Timeline to ethics and data acquisition



Appendix 4-3 Independent Scientific Advisory Committee Protocol Approval – Revised study

ISAC EVALUATION OF PROTOCOLS FOR RESEARCH INVOLVING CPRD DATA

FEEDBACK TO APPLICANTS

CONFIDENTIAL			***by e-mail***
PROTOCOL NO:	16_112		
PROTOCOL TITLE:	Sequelae of gastrointestinal infections: incidence, risk factors, and economic impact on primary and secondary care settings.		
APPLICANT:	Name: Prof. Rafael Perera-Salazar Job Title: Director Medical Statistics Organisation: Nuffield Department Primary Care Health Sciences, University of Oxford E-mail: Rafael.Perera@phc.ox.ac.uk		
APPROVED ☐	**APPROVED WITH COMMENTS (resubmission not required)** ☒	**REVISION/ RESUBMISSION REQUESTED** ☐	**REJECTED** ☐

INSTRUCTIONS:

Please include your response/s to the Reviewer's feedback below only if you are required to Revise/ Resubmit your protocol.

Protocols with an outcome of 'Approved' or 'Approved with comments' do not require resubmission to the ISAC.

REVIEWER COMMENTS:

Protocol 16_112 is approved with the following comments;

1. A practising UK based GP should at the very least be consulted before undertaking any analyses and interpretation of the data.
2. There is a strong possibility of confounding by indication as GPs are more likely to send faecal samples and hence identify the responsible pathogens, in patients presenting with severe disease and/or prior or current use of PPIs. Similar features are also likely to influence the use of antibiotics at presentation.
3. The applicants should acknowledge in the limitations section of the protocol that PPIs are presumably available on non-prescription (OTC) basis
4. The need for patient involvement was not considered in this protocol. Please address all headings in future to prevent un-necessary delays in the review of your application.

DATE OF ISAC FEEDBACK:	06/07/2016
DATE OF APPLICANT FEEDBACK:	

Appendix 4-4 Data files used for thesis

Encrypted CPRD GOLD Data (18 files)

e_16_112_Extract_Additional_001.txt

e_16_112_Extract_Clinical_001-003.txt

e_16_112_Extract_Consultation_001-002.txt

e_16_112_Extract_Immunisation_001.txt

e_16_112_Extract_Patient_001.txt

e_16_112_Extract_Practice_001.txt

e_16_112_Extract_Referral_001.txt

e_16_112_Extract_Staff_001.txt

e_16_112_Extract_Test_001-003.txt

e_16_112_Extract_Therapy_001-003.txt

e_16_112_16_099_Cohort_.txt

Encrypted Linkage data (18 files)

Full Inpatient HES data

HES_acp.txt

e_16_112_HES_diagnosis_epi.txt

e_16_112_HES_diagnosis_hosp.txt

e_16_112_HES_episodes.txt

e_16_112_HES_hospital.txt

e_16_112_HES_hrg.txt

e_16_112_HES_patient.txt

e_16_112_HES_primary_diag_hosp.txt

e_16_112_HES_procedures_epi.txt

Outpatient HES data

e_16_112_hesop_appointment.txt

e_16_112_hesop_clinical.txt

e_16_112_hesop_patient.txt

e_16_112_hesop_patient_pathway.txt

ONS Mortality data

e_16_112_death_patient.txt

Deprivation data

e_16_112_patient_imd2010.txt

e_16_112_prac_imd.txt

LINKAGE ELIGIBILITY FILES

linkage_coverage.txt

e_16_112_linkage_eligibility.txt

Appendix 4-5 Read codes for the selected GI infections by region

Figure 4-4-1 Read codes for *Campylobacter* patients broken down by region for the cohort

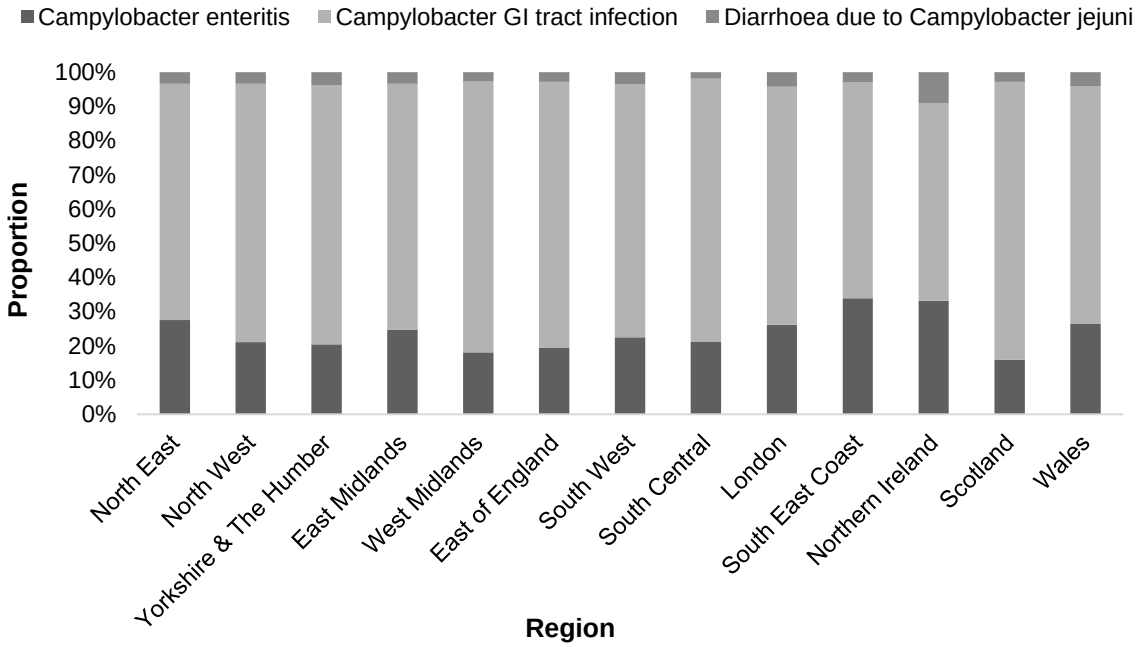
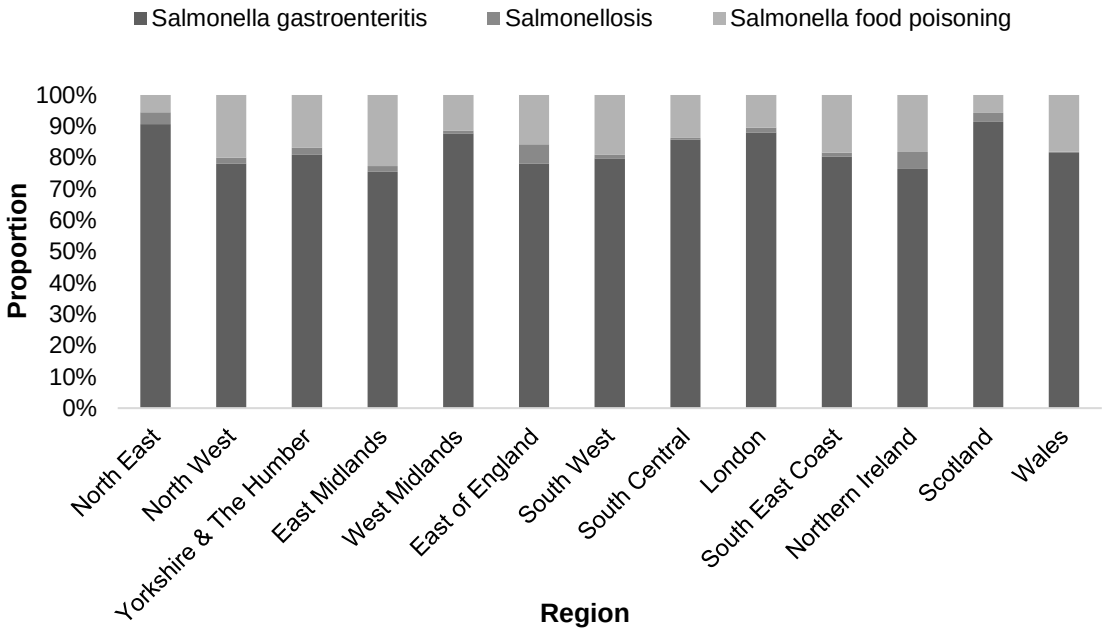


Figure 4-4-2 Read codes for Non-typhoidal *Salmonella* patients broken down by region for the cohort



Appendix 4-6 List of product codes used for exposure selection

Proton pump inhibitors

Prodcode	productname
18	Omeprazole 20mg gastro-resistant capsules
1977	Rabeprazole 10mg gastro-resistant tablets
45173	Omeprazole 20mg gastro-resistant capsules (Almus Pharmaceuticals Ltd)
34302	Omeprazole 20mg gastro-resistant capsules (Generics (UK) Ltd)
42736	Omeprazole 20mg gastro-resistant tablets (Kent Pharmaceuticals Ltd)
41454	Nexium 10mg gastro-resistant granules sachets (AstraZeneca UK Ltd)
31213	Omeran 10mg gastro-resistant tablets (Ranbaxy (UK) Ltd)
13282	Omeprazole 5mg/5ml oral suspension
58475	Rabeprazole 20mg gastro-resistant tablets (Zentiva)
1941	Pariet 20mg gastro-resistant tablets (Eisai Ltd)
49584	Omeprazole 8mg/5ml oral solution
34332	Omeprazole 10mg gastro-resistant capsules (A H Pharmaceuticals Ltd)
57541	Omeprazole 10mg gastro-resistant tablets (Sterwin Medicines)
1947	Zoton 15mg gastro-resistant capsules (Wyeth Pharmaceuticals)
6300	Lansoprazole 30mg orodispersible tablets
5232	Omeprazole 10mg dispersible gastro-resistant tablets
43995	Esomeprazole 20mg gastro-resistant capsules
34843	Omeprazole 20mg gastro-resistant capsules (Dexcel-Pharma Ltd)
53843	Esomeprazole 40mg gastro-resistant tablets (A H Pharmaceuticals Ltd)
60590	Rabeprazole 20mg gastro-resistant tablets (Actavis UK Ltd)
55468	Omeprazole 20mg gastro-resistant capsules (Alliance Healthcare (Distribution) Ltd)
37815	Lansoprazole 30mg gastro-resistant capsules (Sandoz Ltd)
32914	Omeprazole 10mg gastro-resistant tablets (Sandoz Ltd)
6165	Protium 20mg gastro-resistant tablets (Nycomed UK Ltd)
61029	Omeprazole 20mg gastro-resistant capsules (Genesis Pharmaceuticals Ltd)
5178	Esomeprazole 20mg gastro-resistant tablets
53616	Lansoprazole 5mg/5ml oral solution
5358	Lansoprazole 30mg gastro-resistant granules sachets
41501	Esomeprazole 10mg gastro-resistant granules sachets
54188	Lansoprazole 30mg gastro-resistant capsules (Phoenix Healthcare Distribution Ltd)
57504	Zoton FasTab 30mg (Waymade Healthcare Plc)
18225	Esomeprazole 40mg powder for solution for injection vials
35383	Omeprazole 20mg gastro-resistant capsules (Dr Reddy's Laboratories (UK) Ltd)

Prodcode	productname
58344	Omeprazole 50mg/5ml oral suspension
46744	Emozul 20mg gastro-resistant capsules (Consilient Health Ltd)
34812	Omeprazole 20mg Gastro-resistant capsule (Niche Generics Ltd)
52612	Losec 20mg gastro-resistant capsules (Lexon (UK) Ltd)
50365	Omeprazole 8.5mg/5ml oral solution
15275	Omeprazole 10mg gastro-resistant capsules (Teva UK Ltd)
57311	Esomeprazole 20mg gastro-resistant capsules (A H Pharmaceuticals Ltd)
1232	Losec 20mg gastro-resistant capsules (AstraZeneca UK Ltd)
34411	Omeprazole 20mg gastro-resistant capsules (Teva UK Ltd)
26537	Omeran 20mg gastro-resistant tablets (Ranbaxy (UK) Ltd)
25596	Nexium I.V 40mg powder for solution for injection vials (AstraZeneca UK Ltd)
51357	Omeprazole 15mg/5ml oral solution
22709	Losec Infusion 40mg powder for solution for infusion vials (AstraZeneca UK Ltd)
39	Lansoprazole 30mg gastro-resistant capsules
29468	Omeprazole 40mg gastro-resistant capsules (IVAX Pharmaceuticals UK Ltd)
9851	Omeprazole 10mg gastro-resistant tablets
6245	Lansoprazole 15mg orodispersible tablets
58946	Omeprazole 10mg gastro-resistant capsules (Waymade Healthcare Plc)
29422	Losec 40mg Injection (AstraZeneca UK Ltd)
57177	Omeprazole 20mg gastro-resistant capsules (Bristol Laboratories Ltd)
59711	Pantoprazole 20mg gastro-resistant tablets (Teva UK Ltd)
61669	Esomeprazole 40mg gastro-resistant capsules (A H Pharmaceuticals Ltd)
53337	Omeprazole 10mg gastro-resistant capsules (Phoenix Healthcare Distribution Ltd)
10098	Zoton 30mg gastro-resistant granules sachets (Wyeth Pharmaceuticals)
56235	Omeprazole 12.5mg/5ml oral solution
56895	Omeprazole 50mg/5ml oral solution
34984	Heartburn relief 10mg Tablet (A H Pharmaceuticals Ltd)
40759	Lansoprazole 15mg gastro-resistant capsules (Teva UK Ltd)
54939	Lansoprazole 15mg gastro-resistant capsules (Alliance Healthcare (Distribution) Ltd)
57158	Lansoprazole 30mg gastro-resistant capsules (Alliance Healthcare (Distribution) Ltd)
33873	Losec I.V. 40mg powder and solvent for solution for injection vials (AstraZeneca UK Ltd)
9989	Omeprazole 40mg gastro-resistant tablets
6291	Zoton FasTab 15mg (Pfizer Ltd)
54693	Pantoprazole 20mg gastro-resistant tablets (Actavis UK Ltd)
59725	Omeprazole 25mg/5ml oral suspension
56432	Omeprazole 6.8mg/5ml oral solution
42091	Omeprazole 20mg gastro-resistant tablets (Dexcel-Pharma Ltd)
6114	Omeprazole 20mg gastro-resistant tablets

Prodcode	productname
34791	Omeprazole 40mg gastro-resistant capsules (Generics (UK) Ltd)
6490	Nexium 40mg gastro-resistant tablets (AstraZeneca UK Ltd)
6727	Protium 40mg gastro-resistant tablets (Nycomed UK Ltd)
89	Omeprazole 10mg gastro-resistant capsules
49375	Pantoprazole 20mg gastro-resistant tablets (Nycomed UK Ltd)
42533	Omeprazole 20mg gastro-resistant capsules (Focus Pharmaceuticals Ltd)
5269	Nexium 20mg gastro-resistant tablets (AstraZeneca UK Ltd)
5236	Losec MUPS 20mg gastro-resistant tablets (AstraZeneca UK Ltd)
60409	Omeprazole 20mg dispersible gastro-resistant tablets (Waymade Healthcare Plc)
39904	Lansoprazole 15mg gastro-resistant capsules (Sandoz Ltd)
5834	Pariet 10mg gastro-resistant tablets (Eisai Ltd)
24360	Heartburn relief 10mg Tablet (Galpharm International Ltd)
52866	Omeprazole 4mg/5ml oral solution
48063	Lansoprazole 30mg gastro-resistant capsules (Zentiva)
44023	Pantoloc Control 20mg gastro-resistant tablets (Novartis Consumer Health UK Ltd)
41992	Omeprazole 10mg gastro-resistant tablets (Almus Pharmaceuticals Ltd)
30	Lansoprazole 15mg gastro-resistant capsules
62166	Omeprazole 2mg/5ml oral solution
42900	Omeprazole 20mg gastro-resistant tablets (IVAX Pharmaceuticals UK Ltd)
59106	Lansoprazole 30mg/5ml oral solution
44252	Omeprazole 20mg/5ml Oral suspension (Martindale Pharmaceuticals Ltd)
4654	Losec 40mg gastro-resistant capsules (AstraZeneca UK Ltd)
57572	Zoton 15mg gastro-resistant capsules (Dowelhurst Ltd)
17111	Pantoprazole 40mg powder for solution for injection vials
56433	Omeprazole 35mg/5ml oral solution
59296	Rabeprazole 10mg gastro-resistant tablets (Zentiva)
49163	Omeprazole 20mg gastro-resistant capsules (Zentiva)
57528	Losec 20mg gastro-resistant capsules (Dowelhurst Ltd)
34577	Omeprazole 20mg gastro-resistant capsules (Sandoz Ltd)
43057	Lansoprazole 30mg gastro-resistant capsules (Generics (UK) Ltd)
57648	Omeprazole 10mg gastro-resistant capsules (Dr Reddy's Laboratories (UK) Ltd)
51548	Nexium 20mg gastro-resistant tablets (Mawdsley-Brooks & Company Ltd)
42114	Omeran 40mg gastro-resistant tablets (Ranbaxy (UK) Ltd)
7255	Omeprazole 20mg/5ml oral suspension
62031	Lansoprazole 15mg gastro-resistant capsules (DE Pharmaceuticals)
59586	Lansoprazole 30mg gastro-resistant capsules (Kent Pharmaceuticals Ltd)
47511	Omeprazole 5mg/5ml Oral suspension (Martindale Pharmaceuticals Ltd)
6063	Zoton FasTab 30mg (Pfizer Ltd)
519	Zoton 30mg gastro-resistant capsules (Wyeth Pharmaceuticals)
59547	Omeprazole 40mg/5ml oral suspension

Prodcode	productname
50372	Omeprazole 15mg/5ml oral suspension
59404	Lansoprazole 30mg gastro-resistant capsules (Sovereign Medical Ltd)
42382	Lansoprazole 30mg gastro-resistant capsules (Almus Pharmaceuticals Ltd)
25245	Omeprazole 40mg powder and solvent for solution for injection vials
53518	Omeprazole 2mg/5ml oral suspension
35699	Mepradec 10mg gastro-resistant capsules (Discovery Pharmaceuticals Ltd)
60900	Lansoprazole 15mg/5ml oral suspension
5604	Esomeprazole 40mg gastro-resistant tablets
32919	Omeprazole 20mg gastro-resistant tablets (Generics (UK) Ltd)
61504	Esomeprazole 20mg gastro-resistant tablets (Teva UK Ltd)
34571	Omeprazole 10mg gastro-resistant capsules (Sandoz Ltd)
55168	Omeprazole 10mg dispersible gastro-resistant tablets (A H Pharmaceuticals Ltd)
2151	Rabeprazole 20mg gastro-resistant tablets
5419	Pantoprazole 20mg gastro-resistant tablets
55439	Lansoprazole 15mg gastro-resistant capsules (A A H Pharmaceuticals Ltd)
59390	Pantoprazole 40mg gastro-resistant tablets (Nycomed UK Ltd)
34792	Omeprazole 10mg gastro-resistant capsules (Actavis UK Ltd)
55744	Omeprazole 20mg gastro-resistant capsules (Zanza Laboratories Ltd)
43957	Omeprazole 20mg gastro-resistant tablets (Almus Pharmaceuticals Ltd)
51804	Pantoprazole 20mg gastro-resistant tablets (Arrow Generics Ltd)
49433	Omeprazole 40mg/5ml oral solution
57738	Omeprazole 4mg/5ml oral suspension
276	Losec 10mg gastro-resistant capsules (AstraZeneca UK Ltd)
13015	Losec MUPS 10mg gastro-resistant tablets (AstraZeneca UK Ltd)
55700	Omeprazole 3mg/5ml oral suspension
32924	Omeprazole 20mg gastro-resistant tablets (Sandoz Ltd)
4921	Omeprazole 20mg dispersible gastro-resistant tablets
60230	Omeprazole 10mg/5ml oral solution
49209	Lansoprazole 7.5mg/5ml oral solution
42532	Lansoprazole 30mg gastro-resistant capsules (A A H Pharmaceuticals Ltd)
35101	Omeprazole 10mg/5ml oral suspension
9825	Losec MUPS 40mg gastro-resistant tablets (AstraZeneca UK Ltd)
53871	Lansoprazole 30mg gastro-resistant capsules (Actavis UK Ltd)
55745	Losec 10mg gastro-resistant capsules (Lexon (UK) Ltd)
42730	Lansoprazole 30mg gastro-resistant capsules (IVAX Pharmaceuticals UK Ltd)
46745	Emozul 40mg gastro-resistant capsules (Consilient Health Ltd)
44700	Protium I.V. 40mg powder for solution for injection vials (Nycomed UK Ltd)
29457	Omeprazole 20mg gastro-resistant capsules (IVAX Pharmaceuticals UK Ltd)
33326	Omeprazole 10mg gastro-resistant tablets (Teva UK Ltd)
58066	Omeprazole 8mg/5ml oral suspension
30926	Omeprazole 10mg gastro-resistant capsules (IVAX Pharmaceuticals UK Ltd)

Prodcode	productname
1451	Omeprazole 40mg gastro-resistant capsules
33022	Zanprol 10mg gastro-resistant tablets (Omega Pharma Ltd)
36046	Omeprazole 40mg Gastro-resistant capsule (Teva UK Ltd)
1986	Pantoprazole 40mg gastro-resistant tablets
34568	Omeprazole 10mg gastro-resistant capsules (Generics (UK) Ltd)
52971	Losec MUPS 10mg gastro-resistant tablets (Lexon (UK) Ltd)
34967	Omeprazole 20mg gastro-resistant capsules (Actavis UK Ltd)
42898	Omeprazole 10mg gastro-resistant tablets (Actavis UK Ltd)
33565	Omeprazole 20mg Tablet (Neo Laboratories Ltd)
60615	Lansoprazole 30mg orodispersible tablets (A A H Pharmaceuticals Ltd)
43948	Esomeprazole 40mg gastro-resistant capsules
60403	Omeprazole 20mg/5ml oral solution
29835	Omeprazole 40mg powder for solution for infusion vials
58679	Lansoprazole 15mg gastro-resistant capsules (Actavis UK Ltd)
35698	Mepradec 20mg gastro-resistant capsules (Discovery Pharmaceuticals Ltd)
40896	Lansoprazole 30mg gastro-resistant capsules (Teva UK Ltd)
56479	Losec 20mg gastro-resistant capsules (Waymade Healthcare Plc)
60537	Lansoprazole 30mg gastro-resistant capsules (DE Pharmaceuticals)
58030	Rabeprazole 10mg gastro-resistant tablets (Actavis UK Ltd)
58332	Omeprazole 20mg gastro-resistant capsules (Somex Pharma)
60588	Rabeprazole 20mg gastro-resistant tablets (Alliance Healthcare (Distribution) Ltd)
58236	Mezzopram 20mg gastro-resistant tablets (Sandoz Ltd)
50492	Lansoprazole 30mg gastro-resistant capsules (Sigma Pharmaceuticals Plc)
36892	Omeprazole 10mg gastro-resistant tablets (Dexcel-Pharma Ltd)
58216	Omeprazole 20mg gastro-resistant capsules (Kent Pharmaceuticals Ltd)
35257	Omeprazole 40mg gastro-resistant capsules (Dr Reddy's Laboratories (UK) Ltd)
54121	Lansoprazole 15mg/5ml oral solution
51290	Zoton FasTab 15mg (Mawdsley-Brooks & Company Ltd)
57566	Omeprazole 20mg dispersible gastro-resistant tablets (A A H Pharmaceuticals Ltd)
59135	Omeprazole 2.5mg/5ml oral suspension
4955	Omeprazole 40mg dispersible gastro-resistant tablets
44753	Lansoprazole 30mg gastro-resistant capsules (Consilient Health Ltd)
47909	Lansoprazole 30mg gastro-resistant capsules (Arrow Generics Ltd)
52379	Omeprazole 25mg/5ml oral solution
34841	Omeprazole 20mg gastro-resistant capsules (A A H Pharmaceuticals Ltd)
51260	Omeprazole 20mg gastro-resistant capsules (Arrow Generics Ltd)
54683	Mezzopram 10mg gastro-resistant tablets (Sandoz Ltd)
19277	Axid 300mg capsules (Flynn Pharma Ltd)
4885	Axid 150mg Capsule (Eli Lilly and Company Ltd)
28787	Phimetin 200mg Tablet (BHR Pharmaceuticals Ltd)

Antibiotics (Macrolides, Quinolones and Cephalosporins)

prodcode	productname
52029	Zithromax 250mg capsules (Mawdsley-Brooks & Company Ltd)
54903	Clarithromycin 125mg/5ml oral suspension (Alliance Healthcare (Distribution) Ltd)
2429	Erythromycin ethyl succinate 125mg/5ml oral suspension
55589	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)
52502	Fidaxomicin 200mg tablets
58841	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Kent Pharmaceuticals Ltd)
34795	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)
34779	Erythromycin ethyl succinate 125mg/5ml oral suspension (Sandoz Ltd)
46696	Erythromycin ethyl succinate 250mg/5ml oral suspension (Sandoz Ltd)
57267	Clarithromycin 125mg/5ml oral suspension (Waymade Healthcare Plc)
825	Erythroped pi 125mg/5ml Oral suspension (Abbott Laboratories Ltd)
61612	Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Waymade Healthcare Plc)
52719	Clarithromycin 250mg tablets (Apotex UK Ltd)
60263	Erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)
3572	Erythroped 250mg Powder (Abbott Laboratories Ltd)
40784	Clarithromycin 500mg tablets (Sandoz Ltd)
58206	Azithromycin 250mg tablets (Teva UK Ltd)
58902	Clarithromycin 500mg tablets (Phoenix Healthcare Distribution Ltd)
48101	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Focus Pharmaceuticals Ltd)
25751	Erythromycin ethylsuccinate (coated) 250mg/5ml oral suspension sugar free
60805	Clarithromycin 500mg tablets (Waymade Healthcare Plc)
51426	Clarithromycin 500mg tablets (Accord Healthcare Ltd)
53875	Clarithromycin 500mg tablets (Tillomed Laboratories Ltd)
25595	Erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)
45870	Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Pinewood Healthcare)
48163	Clarithromycin 250mg tablets (Actavis UK Ltd)
4153	Erythrolar 250mg/5ml Liquid (Lagap)
50946	Clarithromycin 250mg tablets (Sigma Pharmaceuticals Plc)
58760	Erythroped A 500mg tablets (Necessity Supplies Ltd)

57660 Clarithromycin 250mg tablets (Almus Pharmaceuticals Ltd)
60382 Azithromycin 250mg capsules (DE Pharmaceuticals)
5357 Clarithromycin 250mg/5ml oral suspension
13323 Clarithromycin 500mg powder for solution for infusion vials
9583 Klaricid 250mg/5ml Oral suspension (Abbott Laboratories Ltd)
54897 Clarithromycin 250mg tablets (Tillomed Laboratories Ltd)
681 Clarithromycin 500mg tablets
49978 Erythromycin ethyl succinate 125mg/5ml oral suspension (Focus Pharmaceuticals Ltd)
6121 Klaricid XL 500mg tablets (Abbott Laboratories Ltd)
14171 Erythromycin ethyl succinate 500mg/5ml oral suspension sugar free
54208 Clarithromycin 250mg/5ml oral suspension (Sigma Pharmaceuticals Plc)
54529 Clarithromycin 500mg Modified-release tablet (Hillcross Pharmaceuticals Ltd)
39613 Erythrocin 500 tablets (AMCo)
55148 Clarithromycin 250mg/5ml oral suspension (Alliance Healthcare (Distribution) Ltd)
36544 Arpimycin 125mg/5ml Oral suspension (Rosemont Pharmaceuticals Ltd)
31420 Rovamycin 500mg Tablet (Rhone-Poulenc Rorer Ltd)
53086 Clarithromycin 250mg tablets (DE Pharmaceuticals)
53004 Erythrocin 500 tablets (Necessity Supplies Ltd)
32898 Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)
27504 Primacine 500mg/5ml Liquid (Pinewood Healthcare)
30980 Erythromycin ethyl succinate 500mg/5ml oral suspension (Kent Pharmaceuticals Ltd)
23954 Erythrolar 500mg Tablet (Lagap)
39616 Erythrocin 250 tablets (AMCo)
27768 Erythrolar 250mg Tablet (Lagap)
32902 Erythromycin ethyl succinate 250mg/5ml oral suspension (Kent Pharmaceuticals Ltd)
53688 Clarithromycin 250mg tablets (Ranbaxy (UK) Ltd)
25900 Spiramycin 500mg tablet
33248 Erythromycin 125mg/5ml Liquid (IVAX Pharmaceuticals UK Ltd)
22964 Telithromycin 400mg tablets
61561 Erythromycin ethyl succinate 250mg/5ml oral suspension (Waymade Healthcare Plc)
34974 Clarithromycin 500mg tablets (Teva UK Ltd)
49939 Clarithromycin 500mg tablets (Alliance Healthcare (Distribution) Ltd)
13120 Erythromycin ethyl succinate 250mg/5ml oral suspension (A A H Pharmaceuticals Ltd)
54269 Clarithromycin 250mg tablets (Somex Pharma)
438 Erythromycin stearate 250mg tablets
5057 Azithromycin 200mg/5ml oral suspension
553 Erythromycin 250mg.5ml oral suspension
54098 Erythroped A 500mg tablets (Lexon (UK) Ltd)
60814 Azithromycin 500mg tablets (DE Pharmaceuticals)
765 Clarithromycin 250mg granules sachets
5335 Zithromax 500mg tablets (Pfizer Ltd)

40218 Azithromycin 500mg tablets (Teva UK Ltd)
58037 Clarithromycin 500mg tablets (Almus Pharmaceuticals Ltd)
34650 Clarithromycin 250mg tablets (A A H Pharmaceuticals Ltd)
27495 Arpimycin 125mg/5ml Liquid (Rosemont Pharmaceuticals Ltd)
56203 Erythroped A 500mg tablets (Sigma Pharmaceuticals Plc)
41453 Clarithromycin 125mg/5ml oral suspension (Ranbaxy (UK) Ltd)
201 Erythrocin 1g/vial Injection (Abbott Laboratories Ltd)
53850 Azithromycin 200mg/5ml oral suspension (A A H Pharmaceuticals Ltd)
14511 Erymax sprinkle 125mg Capsule (Elan Pharma)
42659 Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Abbott Laboratories Ltd)
4610 Erythroped forte 500mg/5ml Oral suspension (Abbott Laboratories Ltd)
6623 Klaricid 500 tablets (Abbott Laboratories Ltd)
34811 Clarithromycin 250mg/5ml oral suspension (Ranbaxy (UK) Ltd)
34608 Clarithromycin 500mg tablets (Generics (UK) Ltd)
53179 Clarithromycin 250mg/5ml oral suspension (Sandoz Ltd)
53776 Clarithromycin 500mg tablets (DE Pharmaceuticals)
59036 Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Pinewood Healthcare)
39118 Primacine 250mg/5ml Liquid (Pinewood Healthcare)
51154 Clarithromycin 250mg tablets (Kent Pharmaceuticals Ltd)
52860 Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)
37022 Arpimycin 500mg/5ml Liquid (Rosemont Pharmaceuticals Ltd)
15713 Erythromycin ethylsuccinate 500mg sachets
55428 Clarithromycin 250mg/5ml oral suspension (Waymade Healthcare Plc)
39623 Erythroped PI SF 125mg/5ml oral suspension (AMCo)
50693 Erythrocin 500 tablets (Sigma Pharmaceuticals Plc)
26189 Erythromycin 1g powder for solution for infusion vials
54241 Clarithromycin 250mg/5ml oral suspension (A A H Pharmaceuticals Ltd)
1072 Erythrocin 500 500mg Tablet (Abbott Laboratories Ltd)
61810 Azithromycin 500mg tablets (A A H Pharmaceuticals Ltd)
41389 Erythoden 250mg/5ml Liquid (Stevenden Healthcare)
5116 Azithromycin 250mg capsules
47582 Clarithromycin 250mg tablets (Sandoz Ltd)
54953 Clarithromycin 500mg powder for concentrate for solution for infusion vials (Martindale Pharmaceuticals Ltd)
41584 Erythromycin 250mg/5ml Liquid (IVAX Pharmaceuticals UK Ltd)
2226 Erythromycin ethyl succinate 500mg/5ml oral suspension
53144 Clarithromycin 250mg tablets (Wockhardt UK Ltd)
537 Clarithromycin 250mg tablets
39632 Erythroped A 500mg tablets (AMCo)
2719 Klaricid 250mg tablets (Abbott Laboratories Ltd)

58175 Clarithromycin 500mg tablets (Wockhardt UK Ltd)
49301 Erythrolar 500mg tablets (Ennogen Pharma Ltd)
53703 Clarithromycin 500mg tablets (Kent Pharmaceuticals Ltd)
28289 Klaricid IV 500mg powder for solution for infusion vials (Abbott Laboratories Ltd)
37681 Erythrocin IV lactobionate 1g powder for solution for infusion vials (AMCo)
13167 Erythromycin ethyl succinate 125mg/5ml oral suspension (A A H Pharmaceuticals Ltd)
47242 Erythromycin 250mg/5ml Liquid (C P Pharmaceuticals Ltd)
60308 Erythromycin ethyl succinate 125mg/5ml oral suspension (Alliance Healthcare (Distribution) Ltd)
397 Erythromycin 125mg/5ml oral suspension
993 Erythroped forte 500mg/5ml Liquid (Abbott Laboratories Ltd)
46488 Clarithromycin 500mg tablets (Ranbaxy (UK) Ltd)
16747 Erythroped 250mg Sachets (Abbott Laboratories Ltd)
14514 Zithromax 200mg/5ml oral suspension (Pfizer Ltd)
2225 Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free
12330 Erythromycin ethylsuccinate 1g sachets
30520 Primacine 125mg/5ml Liquid (Pinewood Healthcare)
34394 Clarithromycin 250mg tablets (Generics (UK) Ltd)
2376 Erythromycin ethyl succinate 250mg/5ml oral suspension
2326 Erythromycin 500mg/5ml oral suspension
24220 Arpimycin 250mg/5ml Liquid (Rosemont Pharmaceuticals Ltd)
733 Erythromycin ethyl succinate 500mg tablets
34533 Clarithromycin 250mg tablets (Teva UK Ltd)
13635 Erythromycin ethylsuccinate 250mg sachets
14816 Klaricid Adult 250mg granules sachets (Abbott Laboratories Ltd)
51831 Clarithromycin 125mg/5ml oral suspension (Phoenix Healthcare Distribution Ltd)
33694 Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Generics (UK) Ltd)
54472 Clarithromycin 250mg tablets (Accord Healthcare Ltd)
47126 Erythromycin ethyl succinate 125mg/5ml oral suspension (Pinewood Healthcare)
50948 Erythromycin ethyl succinate 125mg/5ml oral suspension (Phoenix Healthcare Distribution Ltd)
2350 Erythromycin stearate 500mg tablets
105 Erythroped 250mg/5ml Liquid (Abbott Laboratories Ltd)
45795 Clarithromycin 125mg/5ml oral suspension (A A H Pharmaceuticals Ltd)
3736 Klaricid 125mg/5ml Oral suspension (Abbott Laboratories Ltd)
53109 Clarithromycin 500mg tablets (Somex Pharma)
4372 Erythroped forte 500mg Sachets (Abbott Laboratories Ltd)
4165 Zithromax 250mg capsules (Pfizer Ltd)
36514 Arpimycin 250mg/5ml Oral suspension (Rosemont Pharmaceuticals Ltd)
31514 Erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (Abbott Laboratories Ltd)
27203 Erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (Teva UK Ltd)

331 Clarithromycin 125mg/5ml oral suspension
59441 Erythromycin ethyl succinate 125mg/5ml oral suspension (DE Pharmaceuticals)
62143 Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (DE Pharmaceuticals)
34853 Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Teva UK Ltd)
46154 Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (Abbott Laboratories Ltd)
39642 Erythroped Forte SF 500mg/5ml oral suspension (AMCo)
327 Erythroped a 500mg Tablet (Abbott Laboratories Ltd)
53449 Erythrocin 500 tablets (Lexon (UK) Ltd)
53153 Clarithromycin 250mg tablets (Phoenix Healthcare Distribution Ltd)
58756 Erythromycin ethyl succinate 125mg/5ml oral suspension (Waymade Healthcare Plc)
51984 Erythrocin 500 tablets (Mawdsley-Brooks & Company Ltd)
39010 Klaricid Paediatric 250mg/5ml oral suspension (Abbott Laboratories Ltd)
47676 Erythromycin 500mg/5ml Liquid (C P Pharmaceuticals Ltd)
59126 Erythromycin ethyl succinate 125mg/5ml oral suspension (Kent Pharmaceuticals Ltd)
48017 Erythoden 125mg/5ml Liquid (Stevenden Healthcare)
38163 Clarithromycin 500mg tablets (A A H Pharmaceuticals Ltd)
21808 Rommix 125mg/5ml Oral suspension sugar free (Ashbourne Pharmaceuticals Ltd)
45591 Clarie XL 500mg tablets (Teva UK Ltd)
30234 Erythromycin ethylsuccinate 125mg sachets
53398 Clarithromycin 500mg powder for concentrate for solution for infusion vials (Mercury Pharma Group Ltd)
4596 Erythroped a 1g Sachets (Abbott Laboratories Ltd)
52411 Klaricid 250mg tablets (Necessity Supplies Ltd)
4672 Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free
49530 Azithromycin 200mg/5ml oral suspension (Sandoz Ltd)
743 Azithromycin 500mg tablets
39669 Erythroped SF 250mg/5ml oral suspension (AMCo)
9434 Erymin 250mg/5ml Oral suspension (Elan Pharma)
38997 Klaricid Paediatric 125mg/5ml oral suspension (Abbott Laboratories Ltd)
33695 Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Generics (UK) Ltd)
532 Erythroped 250mg/5ml Oral suspension (Abbott Laboratories Ltd)
30177 Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)
61830 Clarithromycin 125mg/5ml oral suspension (Sigma Pharmaceuticals Plc)
33697 Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)
14429 Erythromycin 125mg sprinkle capsules
43400 Clamelle 500mg tablets (Actavis UK Ltd)
61001 Clarithromycin 125mg/5ml oral suspension (Kent Pharmaceuticals Ltd)
48023 Clarithromycin 500mg tablets (Actavis UK Ltd)
52158 Clarithromycin 250mg tablets (Alliance Healthcare (Distribution) Ltd)

50205 Erythrolar 250mg tablets (Ennogen Pharma Ltd)
58426 Azithromycin 500mg tablets (Sandoz Ltd)
46695 Azithromycin 500mg Tablet (Hillcross Pharmaceuticals Ltd)
997 Erythroped pi 125mg/5ml Liquid (Abbott Laboratories Ltd)
3042 Erythroped pi 125mg Sachets (Abbott Laboratories Ltd)
31379 Ketek 400mg tablets (Sanofi)
53168 Clarithromycin 125mg/5ml oral suspension (Sandoz Ltd)
6803 Clarithromycin 500mg modified-release tablets
33888 Azithromycin 250mg tablets
480 Erythrocin 250mg Tablet (Abbott Laboratories Ltd)
34231 Erythromycin 125mg/5ml Liquid (Berk Pharmaceuticals Ltd)
50223 Erythrocin 500 tablets (Stephar (U.K.) Ltd)
33705 Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (Teva UK Ltd)
12277 Cinoxacin 500mg capsules
54393 Ciprofloxacin 250mg tablets (Arrow Generics Ltd)
49839 Ciproxin 500mg tablets (Waymade Healthcare Plc)
32388 Ciproxin 200mg/100ml Infusion (Bayer Plc)
51537 Ciprofloxacin 250mg tablets (Alliance Healthcare (Distribution) Ltd)
47785 Ciprofloxacin 400mg/200ml infusion bags
34494 Ciprofloxacin 500mg tablets (Wockhardt UK Ltd)
50601 Ciprofloxacin 250mg tablets (Accord Healthcare Ltd)
30877 Tarivid 2mg/ml Infusion (Aventis Pharma)
43517 Ciprofloxacin 750mg tablets (Actavis UK Ltd)
56856 Ciprofloxacin 750mg tablets (Ranbaxy (UK) Ltd)
61302 Ciprofloxacin 100mg tablets (Almus Pharmaceuticals Ltd)
7519 Norfloxacin 400mg tablets
7752 Ciproxin 750mg tablets (Bayer Plc)
54663 Ciproxin Infusion 200mg/100ml solution for infusion bottles (Bayer Plc)
58246 Ciprofloxacin 400mg/200ml infusion bags (Hospira UK Ltd)
17693 Tavanic 250mg tablets (Sanofi)
53878 Ciprofloxacin 500mg tablets (Ranbaxy (UK) Ltd)
728 Ciproxin 500mg tablets (Bayer Plc)
58235 Ciprofloxacin 250mg tablets (DE Pharmaceuticals)
56789 Ciprofloxacin 500mg tablets (APC Pharmaceuticals & Chemicals (Europe) Ltd)
59653 Ciproxin Infusion 400mg/200ml solution for infusion bottles (Bayer Plc)
34322 Ciprofloxacin 500mg Tablet (Niche Generics Ltd)
1837 Ciprofloxacin 750mg tablets
34523 Ofloxacin 200mg tablets (Sandoz Ltd)
34973 Ciprofloxacin 750mg Tablet (Niche Generics Ltd)
29343 Ciprofloxacin 250mg tablets (A A H Pharmaceuticals Ltd)
45341 Ciprofloxacin 500mg Tablet (Neo Laboratories Ltd)
47995 Avelox 400mg/250ml solution for infusion bottles (Bayer Plc)

14389 Comprecin 200mg Tablet (Parke-davis Research Laboratories)
6206 Tavanic 500mg tablets (Sanofi)
56012 Levofloxacin 250mg tablets (Dr Reddy's Laboratories (UK) Ltd)
34819 Ofloxacin 400mg tablets (Generics (UK) Ltd)
32112 Norfloxacin 400mg tablets (Genus Pharmaceuticals Ltd)
50055 Ciprofloxacin 500mg tablets (DE Pharmaceuticals)
53673 Levofloxacin 500mg/100ml infusion bags
24373 Tavanic 500mg/100ml solution for infusion vials (Sanofi)
34605 Ciprofloxacin 500mg tablets (Actavis UK Ltd)
55708 Levofloxacin 250mg tablets (Actavis UK Ltd)
45285 Ciprofloxacin 500mg tablets (Teva UK Ltd)
42174 Ciprofloxacin 500mg tablets (IVAX Pharmaceuticals UK Ltd)
52309 Ciprofloxacin 100mg tablets (Sigma Pharmaceuticals Plc)
2726 Tarivid 400mg tablets (Sanofi)
40252 Ofloxacin 200mg/100ml solution for infusion bottles
57960 Ciprofloxacin 500mg tablets (Tillomed Laboratories Ltd)
5238 Levofloxacin 500mg tablets
52099 Ciprofloxacin 750mg tablets (Bristol Laboratories Ltd)
34308 Ciprofloxacin 250mg tablets (Actavis UK Ltd)
52353 Ciproxin 250mg tablets (DE Pharmaceuticals)
163 Ciproxin 250mg/5ml oral suspension (Bayer Plc)
34448 Ciprofloxacin 250mg tablets (Niche Generics Ltd)
57703 Ciprofloxacin 200mg/100ml solution for infusion bottles
53519 Ciproxin 250mg tablets (Lexon (UK) Ltd)
498 Ciprofloxacin 100mg tablets
60436 Ciprofloxacin 250mg tablets (Almus Pharmaceuticals Ltd)
58345 Levofloxacin 250mg tablets (Generics (UK) Ltd)
61783 Ciprofloxacin 250mg tablets (Waymade Healthcare Plc)
56381 Ciprofloxacin 250mg tablets (Co-Pharma Ltd)
48200 Grepafloxacin 400mg Tablet
25901 Sparfloxacin 200mg tablet
58940 Levofloxacin 250mg tablets (A A H Pharmaceuticals Ltd)
52177 Ciproxin 500mg tablets (Sigma Pharmaceuticals Plc)
34391 Ofloxacin 400mg tablets (Sandoz Ltd)
1202 Ciproxin 250mg tablets (Bayer Plc)
34647 Ciprofloxacin 250mg Tablet (Neo Laboratories Ltd)
33989 Ciprofloxacin 250mg tablets (Generics (UK) Ltd)
53641 Ciprofloxacin 500mg tablets (Co-Pharma Ltd)
372 Nalidixic acid 300mg/5ml oral suspension
55917 Ciprofloxacin 500mg tablets (Medreich Plc)
58955 Ciprofloxacin 100mg/50ml solution for infusion vials (A A H Pharmaceuticals Ltd)
561 Ofloxacin 200mg tablets

26840 Ciprofloxacin 100mg/50ml solution for infusion bottles
59572 Ciprofloxacin 500mg tablets (Sigma Pharmaceuticals Plc)
33707 Ofloxacin 400mg tablets (Teva UK Ltd)
33215 Ciprofloxacin 200mg/100ml in sodium chloride 0.9% infusion
6295 Levofloxacin 250mg tablets
30707 Ciprofloxacin 500mg tablets (Generics (UK) Ltd)
10567 Cinobac 500mg Capsule (Eli Lilly and Company Ltd)
58021 Ciprofloxacin 100mg tablets (Dr Reddy's Laboratories (UK) Ltd)
54302 Ciprofloxacin 250mg tablets (Medreich Plc)
11883 Ciprofloxacin 100mg/50ml solution for infusion vials
21147 Uriben 300mg/5ml oral suspension (Rosemont Pharmaceuticals Ltd)
54555 Ciprofloxacin 100mg tablets (DE Pharmaceuticals)
39913 Ciprofloxacin 100mg tablets (Sandoz Ltd)
38171 Ciprofloxacin 200mg/100ml infusion bags
14376 Ciproxin 2mg/ml Infusion (Bayer Plc)
4091 Ciprofloxacin 250mg/5ml oral suspension
34655 Ciprofloxacin 250mg tablets (Wockhardt UK Ltd)
9073 Nalidixic acid with sodium citrate 660mg + 3750mg Sachets
43557 Ciprofloxacin 500mg tablets (PLIVA Pharma Ltd)
29472 Ciprofloxacin 750mg tablets (A A H Pharmaceuticals Ltd)
45263 Ofloxacin 400mg tablets (A A H Pharmaceuticals Ltd)
34694 Ciprofloxacin 250mg tablets (PLIVA Pharma Ltd)
52945 Ciprofloxacin 200mg/100ml solution for infusion vials
281 Ciprofloxacin 250mg tablets
34478 Ciprofloxacin 250mg tablets (Teva UK Ltd)
17272 Teflox 300mg Tablet (Abbott Laboratories Ltd)
49445 Ciprofloxacin 500mg tablets (Almus Pharmaceuticals Ltd)
43814 Ciprofloxacin 250mg tablets (Dr Reddy's Laboratories (UK) Ltd)
61869 Ciproxin 250mg/5ml oral suspension (Waymade Healthcare Plc)
4513 Tarivid 200mg tablets (Sanofi)
10319 Levofloxacin 500mg/100ml Intravenous infusion
28544 Ciprofloxaxin 400mg/200ml in glucose 5% infusion
29507 Ciprofloxacin 400mg/200ml in sodium chloride 0.9% infusion
58608 Ciprofloxacin 100mg tablets (Bristol Laboratories Ltd)
60817 Levofloxacin 500mg tablets (Actavis UK Ltd)
25127 Avelox 400mg tablets (Bayer Plc)
42507 Ciprofloxacin 100mg tablets (A A H Pharmaceuticals Ltd)
17890 Eradacin 150mg Capsule (Sanofi-Synthelabo Ltd)
59937 Ciprofloxacin 750mg tablets (Accord Healthcare Ltd)
21812 Ciproxin Infusion 100mg/50ml solution for infusion bottles (Bayer Plc)
43797 Ciprofloxacin 500mg tablets (Sandoz Ltd)
9154 Ciproxin 100mg tablets (Bayer Plc)

17749 Teflox 400mg Tablet (Abbott Laboratories Ltd)
56439 Ciprofloxacin 200mg/100ml solution for infusion vials (A A H Pharmaceuticals Ltd)
54674 Ciprofloxacin 100mg tablets (Phoenix Healthcare Distribution Ltd)
38006 Ciproxin 400mg/200ml Infusion (Bayer Plc)
583 Ciprofloxacin 500mg tablets
32530 Ciproxin iv flexibag 400mg/200ml Infusion (Bayer Plc)
53088 Ciprofloxacin 500mg tablets (Dr Reddy's Laboratories (UK) Ltd)
54701 Ciprofloxacin 250mg tablets (Bristol Laboratories Ltd)
52501 Ciprofloxacin 500mg tablets (Accord Healthcare Ltd)
23666 Grepafloxacin 600mg Tablet
29280 Ofloxacin 2mg/ml Infusion
41561 Ciprofloxacin 250mg tablets (IVAX Pharmaceuticals UK Ltd)
34541 Ofloxacin 200mg tablets (Teva UK Ltd)
2253 Utinor 400mg tablets (Merck Sharp & Dohme Ltd)
566 Ofloxacin 400mg tablets
58074 Ciprofloxacin 400mg/200ml solution for infusion bottles
35777 Rosoxacin 150mg capsule
12428 Enoxacin 200mg tablets
52807 Ciproxin 500mg tablets (Mawdsley-Brooks & Company Ltd)
34559 Ciprofloxacin 250mg tablets (Sandoz Ltd)
58323 Ciprofloxacin 100mg tablets (Alliance Healthcare (Distribution) Ltd)
18661 Temafloxacin 400mg tablets
10304 Ciprofloxacin 2mg/ml infusion
52616 Ciprofloxacin 500mg tablets (Arrow Generics Ltd)
56075 Levofloxacin 500mg/100ml solution for infusion vials
29458 Ciprofloxacin 500mg tablets (A A H Pharmaceuticals Ltd)
57118 Ciprofloxacin 250mg tablets (Kent Pharmaceuticals Ltd)
54993 Ciprofloxacin 400mg/200ml solution for infusion vials
43123 Moxifloxacin 400mg/250ml solution for infusion bottles
61850 Levofloxacin 500mg tablets (A A H Pharmaceuticals Ltd)
6306 Moxifloxacin 400mg tablets
31000 Kefadim 1g Injection (Eli Lilly and Company Ltd)
10455 Keflex 250mg/5ml Liquid (Eli Lilly and Company Ltd)
5859 Ceporex 500mg/5ml Oral solution (Galen Ltd)
7509 Ceftibuten 400mg capsules
27017 Kiflone 500mg Capsule (Berk Pharmaceuticals Ltd)
21842 Cedax 36mg/ml Liquid (Schering-Plough Ltd)
9520 Cefaclor 250mg Capsule (Lagap)
325 Cefalotin 1g/vial injection
44299 Cefradine 250mg capsules (Kent Pharmaceuticals Ltd)
32642 Cefalexin 125mg/5ml oral suspension (Kent Pharmaceuticals Ltd)
7506 Cefodizime 1g/vial injection

34253 Cefalexin 250mg capsules (A A H Pharmaceuticals Ltd)
55211 Cefaclor 500mg capsules (Kent Pharmaceuticals Ltd)
2661 Ceporex 500mg Capsule (Galen Ltd)
30769 Cefradine 250mg capsules (IVAX Pharmaceuticals UK Ltd)
25953 Kefadol 500mg/vial Injection (Dista Products Ltd)
26989 Kiflone 125mg/5ml Oral solution (Berk Pharmaceuticals Ltd)
29202 Cefalexin 500mg tablets (A A H Pharmaceuticals Ltd)
47983 Cefuroxime 250mg tablets (A A H Pharmaceuticals Ltd)
61661 Cefalexin 125mg/5ml oral suspension (Waymade Healthcare Plc)
23510 Kefadim 500mg powder for solution for injection vials (Flynn Pharma Ltd)
26233 Keftid 125mg/5ml oral suspension (Co-Pharma Ltd)
47993 Cefuroxime (as axetil) 500mg tablets
54864 Cefalexin 250mg capsules (Alliance Healthcare (Distribution) Ltd)
7510 Cefpodoxime 40mg/5ml oral suspension
41106 Ceporex 125mg/5ml syrup (Co-Pharma Ltd)
30046 Claforan 500mg powder for solution for injection vials (Sanofi)
25614 Cefotaxime 2g powder for solution for injection vials
19160 Cefalexin 250mg capsules (Generics (UK) Ltd)
43433 Cefradine 250mg capsules (Teva UK Ltd)
1384 Cefalexin 125mg/5ml suspension
14607 Cefaclor 125mg/5ml Liquid (Lagap)
57842 Cefotaxime 500mg powder for solution for injection vials (Genus Pharmaceuticals Ltd)
33802 Cefalexin 250mg Capsule (Berk Pharmaceuticals Ltd)
26236 Keftid 500mg capsules (Co-Pharma Ltd)
40914 Ceporex 500mg tablets (Co-Pharma Ltd)
28685 Rocephin 2g powder for solution for injection vials (Roche Products Ltd)
9698 Cefalexin 250mg tablets (Teva UK Ltd)
4576 Distaclor 250mg Capsule (Dista Products Ltd)
865 Cefalexin 500mg tablets
32181 Cefalexin 125mg/5ml oral suspension (Actavis UK Ltd)
30772 Cefaclor 250mg capsules (Ranbaxy (UK) Ltd)
8085 Ceporex 500mg Tablet (Galen Ltd)
17129 Orelox 40mg/5ml oral suspension paediatric (Sanofi)
17292 Zinacef 750mg powder for injection vials (GlaxoSmithKline UK Ltd)
41049 Ceporex 250mg tablets (Co-Pharma Ltd)
55897 Ceftazidime 1g powder for solution for injection vials (Generics (UK) Ltd)
17123 Zinacef 1.5g powder for injection vials (GlaxoSmithKline UK Ltd)
52283 Cefalexin 250mg capsules (Arrow Generics Ltd)
58920 Cefuroxime 250mg tablets (Tillomed Laboratories Ltd)
12850 Cefuroxime 125mg tablets
9664 Cefalexin 500mg capsules (IVAX Pharmaceuticals UK Ltd)
36667 Kefadim 2g Infusion (Eli Lilly and Company Ltd)

61881 Ceftazidime 500mg powder for solution for injection vials (A A H Pharmaceuticals Ltd)
54955 Cefalexin 500mg capsules (Milpharm Ltd)
55877 Ceftazidime 2g powder for solution for injection vials (Genus Pharmaceuticals Ltd)
20569 Claforan 1g powder for solution for injection vials (Sanofi)
19138 Cefalexin 500mg capsules (Actavis UK Ltd)
40884 Ceporex 250mg capsules (Co-Pharma Ltd)
26042 Rocephin 250mg powder for solution for injection vials (Roche Products Ltd)
52851 Cefalexin 500mg capsules (Alliance Healthcare (Distribution) Ltd)
3180 Cefaclor 375mg modified-release tablets
7889 Distaclor 375mg Modified-release tablet (Dista Products Ltd)
11989 Keflex 250mg capsules (Flynn Pharma Ltd)
41853 Keftid 250mg/5ml oral suspension (Co-Pharma Ltd)
319 Distaclor 500mg Capsule (Dista Products Ltd)
12065 Cefpodoxime 100mg tablets
9219 Distaclor 250mg/5ml Liquid (Dista Products Ltd)
9157 Keflex 250mg Tablet (Eli Lilly and Company Ltd)
36330 Cefalexin 250mg tablets (Actavis UK Ltd)
17150 Ceporex 125mg/1.25ml Drops (Glaxo Laboratories Ltd)
8625 Ceporex 250mg/5ml Liquid (Galen Ltd)
1306 Suprax 200mg tablets (Sanofi)
34913 Cefaclor 125mg/5ml Oral suspension (Genus Pharmaceuticals Ltd)
19144 Cefalexin 125mg/5ml oral suspension sugar free (Teva UK Ltd)
1038 Cefaclor 125mg/5ml oral suspension
56610 Cefaclor 125mg/5ml oral suspension sugar free (Phoenix Healthcare Distribution Ltd)
20003 Ceftazidime 3g powder for solution for injection vials
53945 Cefalexin 125mg/5ml oral suspension (Alliance Healthcare (Distribution) Ltd)
30610 Nicef 250mg capsules (Co-Pharma Ltd)
41982 Fortum 2g/vial Powder for solution for injection (Glaxo Laboratories Ltd)
400 Cefalexin 500mg capsules
2227 Cefalexin 500mg/5ml oral suspension
59068 Cefuroxime 250mg tablets (Teva UK Ltd)
8019 Ceporex 250mg Tablet (Galen Ltd)
40747 Cefalexin 250mg chewable tablets
24618 Keflex 500mg capsules (Flynn Pharma Ltd)
25666 Cefuroxime with Saline 750mg infusion
6651 Cefalexin 125mg/5ml oral suspension sugar free
41736 Cefalexin 250mg capsules (Kent Pharmaceuticals Ltd)
3737 Cefaclor 250mg/5ml oral suspension
39417 Cefalexin 125mg/5ml oral suspension (Generics (UK) Ltd)
830 Keflex 250mg tablets (Flynn Pharma Ltd)
28054 Zinacef 250mg powder for injection vials (GlaxoSmithKline UK Ltd)
9603 Keflex 500mg Tablet (Eli Lilly and Company Ltd)

34629 Cefradine 500mg capsules (Generics (UK) Ltd)
12554 Cefsulodin 1g/vial sterile powder
7485 Keflex 125mg/5ml Liquid (Eli Lilly and Company Ltd)
47163 Cefalexin 250mg tablets (Arrow Generics Ltd)
34844 Cefradine 500mg capsules (IVAX Pharmaceuticals UK Ltd)
33334 Cefalexin 250mg tablets (A A H Pharmaceuticals Ltd)
43425 Cefaclor 500mg capsules (A A H Pharmaceuticals Ltd)
46973 Cefaclor 250mg/5ml Oral suspension (Genus Pharmaceuticals Ltd)
232 Cefotaxime 500mg powder for solution for injection vials
34543 Cefradine 250mg capsules (A A H Pharmaceuticals Ltd)
26207 Keftid 250mg capsules (Co-Pharma Ltd)
29748 Cefalexin 125mg/5ml oral suspension (A A H Pharmaceuticals Ltd)
27072 Keflex 125mg/5ml oral suspension (Flynn Pharma Ltd)
30530 Ceftazidime with Saline 2g infusion
17873 Fortum 1g powder for solution for injection vials (GlaxoSmithKline UK Ltd)
19838 Ceftriaxone 2g powder for solution for injection vials
32441 Claforan 2g powder for solution for injection vials (Sanofi)
17889 Ceftibuten 90mg/5ml suspension
3523 Distaclor 500mg Modified-release tablet (Dista Products Ltd)
52282 Cefalexin 250mg capsules (Milpharm Ltd)
8008 Ceporex 250mg/5ml Oral solution (Galen Ltd)
34838 Cefaclor 375mg modified-release tablets (A A H Pharmaceuticals Ltd)
41968 Cefalexin 250mg/5ml oral suspension (Teva UK Ltd)
58525 Ceftriaxone 2g powder for solution for infusion vials
16202 Rocephin 1g powder for solution for injection vials (Roche Products Ltd)
41230 Ceporex 500mg/5ml syrup (Co-Pharma Ltd)
7624 Velosef 250mg capsules (Bristol-Myers Squibb Pharmaceuticals Ltd)
19909 Cefuroxime 750mg powder for injection vials
31827 Cefalexin 500mg tablets (IVAX Pharmaceuticals UK Ltd)
8127 Cedax 400mg Capsule (Schering-Plough Ltd)
192 Ceporex 250mg Capsule (Galen Ltd)
1693 Cefalexin 125mg/5ml oral suspension
45221 Cefalexin 250mg/5ml oral suspension (Actavis UK Ltd)
39703 Cefaclor 125mg/5ml oral suspension (A A H Pharmaceuticals Ltd)
725 Cefuroxime 125mg/5ml oral suspension
55895 Ceftriaxone 1g powder for solution for injection vials (PLIVA Pharma Ltd)
48025 Cefaclor 250mg/5ml oral suspension (Ranbaxy (UK) Ltd)
3678 Cefuroxime 250mg tablets
56250 Cefadroxil 500mg capsules (Sandoz Ltd)
36578 Cefalexin 125mg/5ml oral suspension (Ranbaxy (UK) Ltd)
7502 Ceftazidime 2g powder for solution for injection vials
33329 Cefalexin 125mg/5ml oral suspension (Teva UK Ltd)

20992 Distaclor MR 375mg tablets (Flynn Pharma Ltd)
59708 Ceftriaxone 1g powder for solution for injection vials (Genus Pharmaceuticals Ltd)
32221 Kefadim 2g Injection (Eli Lilly and Company Ltd)
366 Cefaclor 250mg capsules
36569 Cefalexin 500mg capsules (Kent Pharmaceuticals Ltd)
10794 Zinnat 125mg tablets (GlaxoSmithKline UK Ltd)
29281 Cefalexin 500mg capsules (Teva UK Ltd)
31110 Keflex 500mg tablets (Flynn Pharma Ltd)
34965 Cefradine 500mg capsules (A A H Pharmaceuticals Ltd)
41192 Cefalexin 250mg/5ml oral suspension (Ranbaxy (UK) Ltd)
59069 Cefalexin 250mg tablets (Phoenix Healthcare Distribution Ltd)
9293 Cefaclor 250mg/5ml oral suspension sugar free
34654 Cefradine 500mg capsules (Teva UK Ltd)
11992 Baxan 500mg capsules (Bristol-Myers Squibb Pharmaceuticals Ltd)
2651 Ceftazidime 1g powder for solution for injection vials
19152 Cefalexin 250mg capsules (Actavis UK Ltd)
20420 Cefaclor 250mg/5ml Liquid (Generics (UK) Ltd)
9690 Cefalexin 250mg capsules (Teva UK Ltd)
4689 Cefaclor 500mg Capsule (Lagap)
58963 Ceftriaxone 2g powder for solution for infusion vials (Kent Pharmaceuticals Ltd)
24046 Ceftazidime 500mg powder for solution for injection vials
18702 Orelox 100mg tablets (Sanofi)
843 Cefixime 200mg tablets
12276 Keflex 500mg Capsule (Eli Lilly and Company Ltd)
26289 Bacticlor MR 375mg tablets (Ranbaxy (UK) Ltd)
25384 Distaclor 125mg/5ml oral suspension (Flynn Pharma Ltd)
7501 Cefotaxime 1g powder for solution for injection vials
52179 Cefadroxil 500mg capsules (Phoenix Healthcare Distribution Ltd)
56444 Ceftriaxone 250mg powder for solution for injection vials (A A H Pharmaceuticals Ltd)
6671 Cefalexin 250mg/5ml oral suspension sugar free
7503 Cefuroxime (as sodium salt) 1.5g/vial infusion
20409 Cefaclor 250mg/5ml Liquid (Lagap)
684 Ceftriaxone 1g powder for solution for injection vials
12235 Ceporex 1g Tablet (Galen Ltd)
7909 Velosef 500mg capsules (Bristol-Myers Squibb Pharmaceuticals Ltd)
1942 Cefadroxil 500mg capsules
60039 Cefalexin 250mg capsules (Waymade Healthcare Plc)
30471 Ceporin 1g Injection (Glaxo Laboratories Ltd)
29464 Cefalexin 250mg/5ml oral suspension (Generics (UK) Ltd)
42008 Cefalexin 250mg/5ml oral suspension (A A H Pharmaceuticals Ltd)
19184 Cefalexin 500mg capsules (Generics (UK) Ltd)
2976 Cefaclor 500mg capsules

3831 Suprax Paediatric 100mg/5ml oral suspension (Sanofi)
61268 Cefuroxime 250mg tablets (Waymade Healthcare Plc)
44755 Cefalexin 500mg Capsule (Berk Pharmaceuticals Ltd)
20549 Cedax 18mg/ml Liquid (Schering-Plough Ltd)
28722 Keflex 250mg/5ml oral suspension (Flynn Pharma Ltd)
31825 Cefalexin 250mg tablets (IVAX Pharmaceuticals UK Ltd)
36599 Cefalexin 250mg capsules (Ranbaxy (UK) Ltd)
32643 Cefalexin 500mg capsules (A A H Pharmaceuticals Ltd)
17871 Fortum 500mg powder for solution for injection vials (GlaxoSmithKline UK Ltd)
43274 Cefotaxime 2g/vial Injection (C P Pharmaceuticals Ltd)
7587 Cefuroxime 250mg powder for injection vials
58623 Cefuroxime 250mg tablets (Alliance Healthcare (Distribution) Ltd)
19133 Cefalexin 250mg capsules (IVAX Pharmaceuticals UK Ltd)
1860 Cefalexin 250mg/5ml oral suspension
21835 Kiflone 250mg Capsule (Berk Pharmaceuticals Ltd)
58239 Ceftriaxone 1g powder for solution for injection vials (A A H Pharmaceuticals Ltd)
3846 Zinnat 250mg tablets (GlaxoSmithKline UK Ltd)
22042 Distaclor 250mg/5ml oral suspension (Flynn Pharma Ltd)
41825 Cefalexin 250mg/5ml Oral solution (C P Pharmaceuticals Ltd)
34133 Cefalexin 250mg/5ml oral suspension sugar free (Teva UK Ltd)
565 Cefradine 250mg capsules
40945 Ceporex 250mg/5ml syrup (Co-Pharma Ltd)
2428 Distaclor 125mg/5ml Liquid (Dista Products Ltd)
8051 Cefaclor 500mg modified-release tablets
30771 Cefaclor 500mg capsules (Ranbaxy (UK) Ltd)
26992 Kiflone 500mg Tablet (Berk Pharmaceuticals Ltd)
30789 Cefradine 250mg capsules (Generics (UK) Ltd)
3609 Ceporex 125mg/5ml Oral solution (Galen Ltd)
21979 Kiflone 250mg/5ml Oral solution (Berk Pharmaceuticals Ltd)
20881 Cefaclor 375mg modified-release tablets (Ranbaxy (UK) Ltd)
59406 Cefalexin 500mg tablets (Waymade Healthcare Plc)
40155 Cefotaxime 1g/vial Injection (C P Pharmaceuticals Ltd)
7526 Cefaclor 125mg/5ml oral suspension sugar free
13910 Cefaclor 125mg/5ml Liquid (Generics (UK) Ltd)
36701 Cefalexin 250mg tablets (Generics (UK) Ltd)
1146 Cefalexin 250mg tablets
59269 Cefalexin 250mg capsules (DE Pharmaceuticals)
19161 Cefalexin 500mg capsules (Ranbaxy (UK) Ltd)
1110 Cefixime 100mg/5ml oral suspension
24090 Cefalexin 250mg capsules (PLIVA Pharma Ltd)
25667 Zinacef 1.5g/vial Infusion (Glaxo Laboratories Ltd)
33605 Nicef 500mg capsules (Co-Pharma Ltd)

17881 Ceftibuten 180mg/5ml suspension
41394 Cefotaxime 500mg/vial Injection (C P Pharmaceuticals Ltd)
18451 Cefalexin 1g tablets
4454 Cefradine 500mg capsules
1713 Cefalexin 250mg/5ml suspension
42070 Kefadim 1g powder for solution for injection vials (Flynn Pharma Ltd)
22321 Cefalexin 500mg tablets (Generics (UK) Ltd)
12248 Cefalexin 125mg/1.25ml paediatric drops
14749 Ceftazidime 2g/vial powder for injection solution
7430 Keflex 250mg Capsule (Eli Lilly and Company Ltd)
58806 Ceftazidime 500mg powder for solution for injection vials (Genus Pharmaceuticals Ltd)
27254 Tenkorex 500mg Capsule (OPD Pharm)
3704 Ceftriaxone 250mg powder for solution for injection vials
155 Cefalexin 250mg capsules
290 Cefuroxime 1.5g powder for injection vials
60202 Cefalexin 250mg/5ml oral suspension (Kent Pharmaceuticals Ltd)
32750 Moxalactam 1g/vial Injection (Eli Lilly and Company Ltd)
62188 Cefalexin 250mg capsules (Phoenix Healthcare Distribution Ltd)
61418 Cefadroxil 500mg capsules (Sigma Pharmaceuticals Plc)
58463 Cefuroxime 250mg tablets (Sandoz Ltd)
13412 Zinnat 125mg/5ml oral suspension (GlaxoSmithKline UK Ltd)
9689 Cefalexin 500mg tablets (Teva UK Ltd)
18243 Distaclor 500mg capsules (Flynn Pharma Ltd)
7560 Ceporex 125mg/5ml Liquid (Galen Ltd)
32235 Cefaclor 125mg/5ml oral suspension (Ranbaxy (UK) Ltd)
40915 Ceporex 500mg capsules (Co-Pharma Ltd)

Appendix 4-7 List of read codes used for outcome selection in CPRD

medcode	readcode	readterm
451	J521.11	Irritable bowel syndrome
1796	J4...12	Inflammatory bowel disease
2194	A993.11	Reiter's syndrome
8103	A993.00	Reiter's disease / syndrome
73751	N03xF00	Arthritis associated with other disease, talonavicular joint
92962	N03x200	Arthritis associated with other disease, acromioclavic joint
99026	N03xG00	Arthritis associated with other disease, other tarsal joint
72011	N03xH00	Arthritis associated with other disease, 1st MTP joint
96400	N03xE00	Arthritis associated with other disease, subtalar joint
57901	N03x600	Arthritis associated with other disease, MCP joint
94590	N03x100	Arthritis associated with other disease, sternoclavic joint
73774	N03x800	Arthritis associated with other disease, DIP joint of finger
73413	N03x400	Arthritis associated with other disease, dist rad-uln joint
73716	N03x700	Arthritis associated with other disease, PIP joint of finger
100356	N03xA00	Arthritis associated with other disease, sacro-iliac joint

1607	F370000	Guillain-Barre syndrome
704	J410100	Ulcerative colitis
1796	J4….12	Inflammatory bowel disease

Appendix 4-8 List of ICD-9 and ICD-10 codes for outcome selection in HES and ONS data

Appendix 4-8-1 List of ICD-9 codes used for outcome selection in HES and ONS data

ICD-9 code	Condition
995.91	Sepsis
001-009	Intestinal infectious diseases
357.4	Inflammatory polyneuropathy
357.0	Guillian-Barre syndrome
543*	Diseases of appendix
555*	Crohn's disease
556*	Ulcerative colitis
558	Other and unspecified noninfective gastroenteritis and colitis
564.1	Irritable bowel syndrome
564	Other functional intestinal disorders
560.2, 560.9, 569.89,751.1, 751.5, 555.2,	Other diseases of intestine

557.0, 230.7, 152	
711	Infectious athropathies
714	Rheumatoid arthritis with rheumatoid factor

Appendix 4-8-2 List of ICD-10 codes used for outcome selection in HES and ONS data

ICD-10 code	Condition
A41.5	Sepsis due to other Gram-negative organisms
A00-A09	Intestinal infectious diseases
G61	Inflammatory polyneuropathy
G61.0	Guillian-Barre syndrome
I30	Acute pericarditis
I31	Other diseases of pericardium
I32	Pericarditis in diseases clasifies elsewhere
I33	Acute and subacute endocarditis
I38	Endocarditis, valve unspecified
I39	Endocarditis and heart valve disorders in diseases classified elsewhere
I40	Acute myocarditis
I41	Myocarditis in diseases classified elsewhere
K35-K38	Diseases of appendix
K55	Vascular disorders of intestines
K58	Irritable bowel syndrome
K59	Other functional intestinal disorders
K63	Other diseases of intestine
K55-K64	Other diseases of intestine
M00-M03	Infectious athropathies

U82-
U84 Resistance to antimicrobial drugs

Appendix 4-9 Charlson comorbidity index and Read codes in CPRD

charlson_index	medcode	readcode	readterm
1	17345	G714.11	AAA - Abdominal aortic aneurysm without mention of rupture
1	17767	G713.00	Abdominal aortic aneurysm which has ruptured
1	1867	G714.00	Abdominal aortic aneurysm without mention of rupture
1	41020	66YC.00	Absent from work or school due to asthma
6	36294	A788z00	Acquired human immunodeficiency virus infection syndrome NOS
6	23770	A788.00	Acquired immune deficiency syndrome
1	68277	N001.11	Acrosclerosis
1	12229	G30X000	Acute ST segment elevation myocardial infarction
1	12139	G300.00	Acute anterolateral infarction
1	17872	G301100	Acute anteroseptal infarction
1	23707	G580000	Acute congestive heart failure
1	18027	J120.00	Acute duodenal ulcer
1	53797	J120z00	Acute duodenal ulcer NOS
1	53822	J120y00	Acute duodenal ulcer unspecified
1	18001	J120100	Acute duodenal ulcer with haemorrhage
1	48730	J120300	Acute duodenal ulcer with haemorrhage and perforation
1	73417	J120400	Acute duodenal ulcer with obstruction
1	18324	J120200	Acute duodenal ulcer with perforation
1	44335	J120000	Acute duodenal ulcer without mention of complication
2	42539	B670.00	Acute erythraemia and erythroleukaemia
1	185	H333.00	Acute exacerbation of asthma

1	24040	J110.00	Acute gastric ulcer
1	44324	J110z00	Acute gastric ulcer NOS
1	24342	J110y00	Acute gastric ulcer unspecified
1	30054	J110100	Acute gastric ulcer with haemorrhage
1	71403	J110300	Acute gastric ulcer with haemorrhage and perforation
1	109546	J110400	Acute gastric ulcer with obstruction
1	14671	J110200	Acute gastric ulcer with perforation
1	64165	J110000	Acute gastric ulcer without mention of complication
1	45184	J140.00	Acute gastrojejunal ulcer
1	42274	J140z00	Acute gastrojejunal ulcer NOS
1	96628	J140100	Acute gastrojejunal ulcer with haemorrhage
1	106330	J140300	Acute gastrojejunal ulcer with haemorrhage and perforation
1	102177	J140200	Acute gastrojejunal ulcer with perforation
1	27964	G582.00	Acute heart failure
1	8935	G302.00	Acute inferolateral infarction
1	29643	G303.00	Acute inferoposterior infarction
1	5255	G581000	Acute left ventricular failure
2	4072	B680.00	Acute leukaemia NOS
2	4251	B640.00	Acute lymphoid leukaemia
2	19974	B660.00	Acute monocytic leukaemia
2	28276	B675.00	Acute myelofibrosis
2	4413	B650.00	Acute myeloid leukaemia
2	61500	B690.00	Acute myelomonocytic leukaemia
1	241	G30..00	Acute myocardial infarction
1	14658	G30z.00	Acute myocardial infarction NOS

2	67460	K001.00	Acute nephritis with lesions of necrotising glomerulitis
1	9507	G307000	Acute non-Q wave infarction
1	10562	G307100	Acute non-ST segment elevation myocardial infarction
2	50858	B674.00	Acute panmyelosis
1	32856	J130.00	Acute peptic ulcer
1	50048	J130z00	Acute peptic ulcer NOS
1	67711	J130y00	Acute peptic ulcer unspecified
1	44637	J130100	Acute peptic ulcer with haemorrhage
1	45304	J130300	Acute peptic ulcer with haemorrhage and perforation
1	5521	J130200	Acute peptic ulcer with perforation
1	68661	J130000	Acute peptic ulcer without mention of complication
2	27664	B65y100	Acute promyelocytic leukaemia
2	64482	K101000	Acute pyelonephritis without medullary necrosis
2	46242	K041.00	Acute renal cortical necrosis
2	25582	K04z.00	Acute renal failure NOS
2	31369	K042.00	Acute renal medullary necrosis
1	3704	G307.00	Acute subendocardial infarction
1	92955	H32y000	Acute vesicular emphysema
1	53704	J600200	Acute yellow atrophy
1	7059	8H2J.00	Admit diabetic emergency
1	32898	8H2S.00	Admit heart failure emergency
2	37461	B64y200	Adult T-cell leukaemia
2	10099	F420300	Advanced diabetic maculopathy
1	4743	J612.00	Alcoholic cirrhosis of liver
1	46977	H35z.00	Allergic alveolitis and pneumonitis NOS

1	53095	H35zz00	Allergic alveolitis and pneumonitis NOS
1	21232	H33zz12	Allergic asthma NEC
1	18207	H33zz13	Allergic bronchitis NEC
2	9491	B142.11	Anal carcinoma
2	108667	B1z1000	Angiosarcoma of spleen
1	63001	J112.00	Anti-platelet induced gastric ulcer
1	1735	G71..00	Aortic aneurysm
1	6872	G71z.00	Aortic aneurysm NOS
1	1736	7A14.11	Aortic aneurysm repair
1	16034	G716.00	Aortic aneurysm without mention of rupture NOS
1	19477	E004.00	Arteriosclerotic dementia
1	42279	E004z00	Arteriosclerotic dementia NOS
1	56912	E004100	Arteriosclerotic dementia with delirium
1	43292	E004300	Arteriosclerotic dementia with depression
1	55467	E004200	Arteriosclerotic dementia with paranoia
1	8303	H41..00	Asbestosis
1	51410	H41z.00	Asbestosis NOS
1	41017	1780.00	Aspirin induced asthma
1	78	H33..00	Asthma
1	13066	663h.00	Asthma - currently dormant
	232	H33z100	Asthma attack
1	8335	H33z111	Asthma attack NOS
1	31225	663t.00	Asthma causes daytime symptoms 1 to 2 times per month
1	24884	663u.00	Asthma causes daytime symptoms 1 to 2 times per week
1	26503	663v.00	Asthma causes daytime symptoms most days

1	39570	663r.00	Asthma causes night symptoms 1 to 2 times per month
1	30815	663N000	Asthma causing night waking
1	11370	1O2..00	Asthma confirmed
1	42824	663q.00	Asthma daytime symptoms
1	7416	663N.00	Asthma disturbing sleep
1	38146	663N100	Asthma disturbs sleep weekly
1	7191	663P.00	Asthma limiting activities
1	38144	663w.00	Asthma limits walking up hills or stairs
1	8355	9OJA.11	Asthma monitored
1	26501	663s.00	Asthma never causes daytime symptoms
1	26504	663f.00	Asthma never restricts exercise
1	31167	66YP.00	Asthma night-time symptoms
1	7229	663W.00	Asthma prophylactic medication used
1	25181	663e.00	Asthma restricts exercise
1	26506	663e100	Asthma severely restricts exercise
1	26861	663e000	Asthma sometimes restricts exercise
1	19519	663p.00	Asthma treatment compliance unsatisfactory
1	4442	H33z.00	Asthma unspecified
6	58859	A788100	Asymptomatic human immunodeficiency virus infection
1	70787	H32y100	Atrophic (senile) emphysema
1	46529	9OJ1.00	Attends asthma monitoring
1	62200	H351.00	Bagassosis
1	92695	7612111	Balfour excision of gastric ulcer
1	94894	H431.00	Bauxite fibrosis of lung
1	49194	H432.00	Berylliosis

1	9494	J616.00	Biliary cirrhosis
1	58630	J616z00	Biliary cirrhosis NOS
1	27345	H352.00	Bird-fancier's lung
1	36240	H352z00	Bird-fancier's lung NOS
1	11124	J110111	Bleeding acute gastric ulcer
1	18625	J121111	Bleeding chronic duodenal ulcer
1	36583	J111111	Bleeding chronic gastric ulcer
1	40823	H334.00	Brittle asthma
1	1555	H33..11	Bronchial asthma
1	2195	H34..00	Bronchiectasis
1	32679	H34z.00	Bronchiectasis NOS
1	3480	H30z.00	Bronchitis NOS
1	38639	H460.00	Bronchitis and pneumonitis due to chemical fumes
1	55758	H460z00	Bronchitis and pneumonitis due to chemical fumes NOS
1	148	H30..00	Bronchitis unspecified
1	54822	H352000	Budgerigar-fanciers' lung
2	21402	B602.00	Burkitt's lymphoma
2	71304	B602z00	Burkitt's lymphoma NOS
2	97577	B602300	Burkitt's lymphoma of intra-abdominal lymph nodes
2	100006	B602200	Burkitt's lymphoma of intrathoracic lymph nodes
2	59115	B602100	Burkitt's lymphoma of lymph nodes of head, face and neck
2	92380	B602500	Burkitt's lymphoma of lymph nodes of inguinal region and leg
1	37365	H440.00	Byssinosis
1	3540	1761.00	C/O bronchial catarrh
1	6960	G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage

2	348	B34..11	Ca female breast
2	11628	B1z0.11	Cancer of bowel
2	1986	B440.11	Cancer of ovary
2	2755	B....11	Cancers
1	26442	H441.00	Cannabinosis
1	56838	N04y011	Caplan's syndrome
2	36495	B161211	Carcinoma common bile duct
2	31393	B160.11	Carcinoma gallbladder
2	9902	B3...11	Carcinoma of bone, connective tissue, skin and breast
2	22163	B134.11	Carcinoma of caecum
2	3357	B1...11	Carcinoma of digestive organs and peritoneum
2	16874	B4...11	Carcinoma of genitourinary organ
2	9984	B00..11	Carcinoma of lip
2	24374	B0...11	Carcinoma of lip, oral cavity and pharynx
2	8693	B5...11	Carcinoma of other and unspecified sites
2	7219	B141.11	Carcinoma of rectum
2	45307	B2...11	Carcinoma of respiratory tract and intrathoracic organs
6	6170	B590.11	Carcinomatosis
1	1223	G58..11	Cardiac failure
1	17278	G58z.12	Cardiac failure NOS
1	24503	8B29.00	Cardiac failure therapy
1	27438	J615700	Cardiac portal cirrhosis
1	30421	G30..13	Cardiac rupture following myocardial infarction (MI)
1	10980	H322.00	Centrilobular emphysema
1	13564	G613.00	Cerebellar haemorrhage

1	54744	F11x200	Cerebral degeneration due to cerebrovascular disease
1	27975	G641000	Cerebral infarction due to embolism of cerebral arteries
6	5199	B583200	Cerebral metastasis
2	10851	B51..11	Cerebral tumour - malignant
1	2418	G6...00	Cerebrovascular disease
1	10062	G6z..00	Cerebrovascular disease NOS
2	3230	B41..11	Cervical carcinoma (uterus)
1	17359	H30..11	Chest infection - unspecified bronchitis
1	1208	H330.12	Childhood asthma
2	52327	B653000	Chloroma
2	5062	B30..11	Chondroma
2	28003	B420.00	Choriocarcinoma
2	56893	K0A3300	Chron neph syn difus mesangial prolifrtiv glomerulonephritis
2	57168	K0A3200	Chron nephritic syndrom difuse membranous glomerulonephritis
1	9029	J614100	Chronic active hepatitis
1	1755	J614200	Chronic aggressive hepatitis
1	7602	J617000	Chronic alcoholic hepatitis
1	5798	H312000	Chronic asthmatic bronchitis
1	3243	H31..00	Chronic bronchitis
1	15157	H31z.00	Chronic bronchitis NOS
1	26306	H320.00	Chronic bullous emphysema
1	23492	H320z00	Chronic bullous emphysema NOS
1	15626	H310000	Chronic catarrhal bronchitis
1	32671	G580100	Chronic congestive heart failure

2	65400	K02y300	Chronic diffuse glomerulonephritis
1	9853	J121.00	Chronic duodenal ulcer
1	51406	J121z00	Chronic duodenal ulcer NOS
1	52138	J121y00	Chronic duodenal ulcer unspecified
1	71881	J121300	Chronic duodenal ulcer with haemorrhage and perforation
1	44073	J121400	Chronic duodenal ulcer with obstruction
1	33438	J121000	Chronic duodenal ulcer without mention of complication
1	64721	H464000	Chronic emphysema due to chemical fumes
2	100786	B651000	Chronic eosinophilic leukaemia
2	37468	B671.00	Chronic erythraemia
2	4669	K02y200	Chronic focal glomerulonephritis
1	18654	J111.00	Chronic gastric ulcer
1	44309	J111z00	Chronic gastric ulcer NOS
1	64556	J111y00	Chronic gastric ulcer unspecified
1	63582	J111100	Chronic gastric ulcer with haemorrhage
1	71897	J111300	Chronic gastric ulcer with haemorrhage and perforation
1	67356	J111400	Chronic gastric ulcer with obstruction
1	53336	J111200	Chronic gastric ulcer with perforation
1	48946	J111000	Chronic gastric ulcer without mention of complication
1	96090	J141.00	Chronic gastrojejunal ulcer
1	110244	J141300	Chronic gastrojejunal ulcer with haemorrhage and perforation
2	7804	K02..00	Chronic glomerulonephritis
2	97758	K02y000	Chronic glomerulonephritis + diseases EC
2	15097	K02z.00	Chronic glomerulonephritis NOS
2	31701	B651.11	Chronic granulocytic leukaemia

1	1754	J614.00	Chronic hepatitis
1	15489	J614z00	Chronic hepatitis NOS
1	53877	J614y00	Chronic hepatitis unspecified
2	29013	1Z10.00	Chronic kidney disease stage 1
2	12586	1Z11.00	Chronic kidney disease stage 2
2	12566	1Z12.00	Chronic kidney disease stage 3
2	12479	1Z13.00	Chronic kidney disease stage 4
2	12585	1Z14.00	Chronic kidney disease stage 5
2	16416	B681.00	Chronic leukaemia NOS
2	27790	B641.11	Chronic lymphatic leukaemia
2	8625	B641.00	Chronic lymphoid leukaemia
2	61494	K022.00	Chronic membranoproliferative glomerulonephritis
2	10809	K021.00	Chronic membranous glomerulonephritis
2	27458	B661.00	Chronic monocytic leukaemia
2	10726	B651.00	Chronic myeloid leukaemia
2	27520	B651z00	Chronic myeloid leukaemia NOS
2	22050	B691.00	Chronic myelomonocytic leukaemia
2	73026	K0A3500	Chronic neph syn difus mesangiocapillary glomerulonephritis
2	60857	K0A3700	Chronic nephritic syn diffuse crescentic glomerulonephritis
2	102783	B651200	Chronic neutrophilic leukaemia
1	37247	H3z..11	Chronic obstructive pulmonary disease NOS
1	40997	J131.00	Chronic peptic ulcer
1	69663	J131z00	Chronic peptic ulcer NOS
1	70390	J131y00	Chronic peptic ulcer unspecified
1	53126	J131100	Chronic peptic ulcer with haemorrhage

1	52313	J131400	Chronic peptic ulcer with obstruction
1	37620	J131200	Chronic peptic ulcer with perforation
1	99430	J131000	Chronic peptic ulcer without mention of complication
1	23578	J614000	Chronic persistent hepatitis
1	47782	H464200	Chronic pulmonary fibrosis due to chemical fumes
1	22536	H4y1000	Chronic pulmonary fibrosis following radiation
2	57568	K100100	Chronic pyelonephritis with medullary necrosis
2	99631	K100000	Chronic pyelonephritis without medullary necrosis
2	65064	K023.00	Chronic rapidly progressive glomerulonephritis
2	512	K05..00	Chronic renal failure
1	45089	H31y100	Chronic tracheobronchitis
1	5909	H312011	Chronic wheezy bronchitis
1	16725	J615.00	Cirrhosis - non alcoholic
1	6863	J61..00	Cirrhosis and chronic liver disease
1	1638	J615z13	Cirrhosis of liver NOS
1	6853	G73z011	Claudication
1	38304	S620.00	Closed traumatic subarachnoid haemorrhage
1	64014	761J100	Closure of gastric ulcer NEC
1	4741	7627000	Closure of perforated duodenal ulcer
1	20677	761J000	Closure of perforated gastric ulcer
1	19492	H40..00	Coal workers' pneumoconiosis
2	9118	B13z.11	Colonic cancer
1	11424	G580300	Compensated cardiac failure
1	54893	H582.00	Compensatory emphysema
2	37160	F230000	Congenital paraplegia

1	2906	G580.11	Congestive cardiac failure
1	5141	G554000	Congestive cardiomyopathy
1	398	G580.00	Congestive heart failure
1	2491	G30..12	Coronary thrombosis
1	18739	J615z12	Cryptogenic cirrhosis of liver
1	27884	G580200	Decompensated cardiac failure
1	25386	E041.00	Dementia in conditions EC
2	24375	B339.00	Dermatofibrosarcoma protuberans
1	47684	H47y000	Detergent asthma
2	27340	B670.11	Di Guglielmo's disease
1	711	C10..00	Diabetes mellitus
1	72345	C102z00	Diabetes mellitus NOS with hyperosmolar coma
1	42505	C101z00	Diabetes mellitus NOS with ketoacidosis
1	65062	C103z00	Diabetes mellitus NOS with ketoacidotic coma
2	22573	C106z00	Diabetes mellitus NOS with neurological manifestation
1	50972	C100z00	Diabetes mellitus NOS with no mention of complication
2	34283	C105z00	Diabetes mellitus NOS with ophthalmic manifestation
1	70821	C10yz00	Diabetes mellitus NOS with other specified manifestation
1	65025	C107z00	Diabetes mellitus NOS with peripheral circulatory disorder
1	64357	C10zz00	Diabetes mellitus NOS with unspecified complication
1	36695	C10D.00	Diabetes mellitus autosomal dominant type 2
1	61122	C10H.00	Diabetes mellitus induced by non-steroid drugs
1	32403	C107.11	Diabetes mellitus with gangrene
1	21482	C102.00	Diabetes mellitus with hyperosmolar coma
1	1682	C101.00	Diabetes mellitus with ketoacidosis

1	15690	C103.00	Diabetes mellitus with ketoacidotic coma
2	35107	C104z00	Diabetes mellitus with nephropathy NOS
2	16230	C106.00	Diabetes mellitus with neurological manifestation
2	7795	C106.12	Diabetes mellitus with neuropathy
1	38986	C100.00	Diabetes mellitus with no mention of complication
2	33254	C105.00	Diabetes mellitus with ophthalmic manifestation
1	33343	C10y.00	Diabetes mellitus with other specified manifestation
1	35399	C107.00	Diabetes mellitus with peripheral circulatory disorder
2	16491	C106.13	Diabetes mellitus with polyneuropathy
1	45491	C10z.00	Diabetes mellitus with unspecified complication
2	39317	C106100	Diabetes mellitus, adult onset, + neurological manifestation
2	41389	C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
1	63762	C10z100	Diabetes mellitus, adult onset, + unspecified complication
1	14803	C100100	Diabetes mellitus, adult onset, no mention of complication
1	43139	C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
1	54856	C101100	Diabetes mellitus, adult onset, with ketoacidosis
1	33807	C107200	Diabetes mellitus, adult with gangrene
1	63371	C10y100	Diabetes mellitus, adult, + other specified manifestation
1	63357	C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
1	70448	C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder
2	69748	C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation
1	24490	C100000	Diabetes mellitus, juvenile type, no mention of complication
1	40023	C102000	Diabetes mellitus, juvenile type, with hyperosmolar coma
1	53200	C101000	Diabetes mellitus, juvenile type, with ketoacidosis
1	42567	C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma

2	93922	C104000	Diabetes mellitus, juvenile type, with renal manifestation
1	32556	C107.12	Diabetes with gangrene
1	43951	66AK.00	Diabetic - cooperative patient
1	13071	66AI.00	Diabetic - good control
1	2378	66AJ.00	Diabetic - poor control
1	22023	66AJz00	Diabetic - poor control NOS
2	59903	C106.11	Diabetic amyotrophy
2	2340	F381311	Diabetic amyotrophy
1	6125	66AS.00	Diabetic annual review
2	10659	F464000	Diabetic cataract
2	3837	F420400	Diabetic maculopathy
2	37315	F3y0.00	Diabetic mononeuropathy
2	2475	C104.11	Diabetic nephropathy
2	2342	F372.12	Diabetic neuropathy
1	8842	66A5.00	Diabetic on insulin
1	28769	66AV.00	Diabetic on insulin and oral treatment
1	34152	G73y000	Diabetic peripheral angiopathy
2	5002	F372.11	Diabetic polyneuropathy
2	1323	F420.00	Diabetic retinopathy
2	11626	F420z00	Diabetic retinopathy NOS
1	24363	8A13.00	Diabetic stabilisation
1	3450	J615300	Diffuse nodular cirrhosis
2	50695	B627500	Diffuse non-Hodgkin mixed sml & lge cell (diffuse) lymphoma
2	70509	B627D00	Diffuse non-Hodgkin's centroblastic lymphoma

2	53551	B627600	Diffuse non-Hodgkin's immunoblastic (diffuse) lymphoma
2	17460	B627700	Diffuse non-Hodgkin's lymphoblastic (diffuse) lymphoma
2	65180	B627800	Diffuse non-Hodgkin's lymphoma undifferentiated (diffuse)
2	39798	B627X00	Diffuse non-Hodgkin's lymphoma, unspecified
2	50668	B627300	Diffuse non-Hodgkin's small cell (diffuse) lymphoma
2	108182	B627400	Diffuse non-Hodgkin's small cleaved cell (diffuse) lymphoma
1	16521	G710.00	Dissecting aortic aneurysm
1	20007	N000000	Disseminated lupus erythematosus
6	13569	B590.00	Disseminated malignancy NOS
1	36942	N000200	Drug-induced systemic lupus erythematosus
1	3462	J123.00	Duodenal erosion
1	352	J12..00	Duodenal ulcer - (DU)
1	15175	J12z.00	Duodenal ulcer NOS
1	22918	J122.00	Duodenal ulcer disease
1	7058	8H2P.00	Emergency admission, asthma
1	17220	7A13.11	Emergency repair of aortic aneurysm
1	794	H32..00	Emphysema
1	33450	H32z.00	Emphysema NOS
1	14798	H312100	Emphysematous bronchitis
2	6712	K050.00	End stage renal failure
1	96456	N060.11	Endemic polyarthritis
1	63718	761D600	Endoscopic injection haemostasis of gastric ulcer
2	5034	B33..12	Epithelioma
1	7017	7004300	Evacuation of intracerebral haematoma NEC
1	5867	173A.00	Exercise induced asthma

1	4606	H33zz11	Exercise induced asthma
1	7146	H330.00	Extrinsic (atopic) asthma
1	11312	H35..00	Extrinsic allergic alveolitis
1	45782	H330z00	Extrinsic asthma NOS
1	6707	H330111	Extrinsic asthma with asthma attack
1	14777	H330000	Extrinsic asthma without status asthmaticus
1	15588	H350.00	Farmers' lung
1	44676	J615400	Fatty portal cirrhosis
1	23552	N041.00	Felty's syndrome
1	37959	H311100	Fetid chronic bronchitis
2	72224	B1z1100	Fibrosarcoma of spleen
1	28853	N04y012	Fibrosing alveolitis associated with rheumatoid arthritis
2	39085	F220.00	Flaccid hemiplegia
2	46175	F241000	Flaccid paraplegia
1	8350	N040T00	Flare of rheumatoid arthritis
1	68376	J612.11	Florid cirrhosis
2	67995	K032000	Focal membranoproliferative glomerulonephritis
2	17182	B627C11	Follicular lymphoma NOS
2	70842	B627100	Follicular non-Hodg mixed sml cleavd & lge cell lymphoma
2	49262	B627200	Follicular non-Hodgkin's large cell lymphoma
2	21549	B627C00	Follicular non-Hodgkin's lymphoma
2	28639	B627000	Follicular non-Hodgkin's small cleaved cell lymphoma
1	39949	G732200	Gangrene of finger
1	12735	G732100	Gangrene of foot
1	23672	G732400	Gangrene of hand

1	51057	G732300	Gangrene of thumb
1	5414	G732000	Gangrene of toe
2	10368	B11..11	Gastric neoplasm
1	1262	J11..00	Gastric ulcer - (GU)
1	29771	J11z.00	Gastric ulcer NOS
1	64913	J14..12	Gastrocolic ulcer
1	23082	J14..00	Gastrojejunal ulcer (GJU)
1	15403	J14z.00	Gastrojejunal ulcer NOS
1	12555	G671z00	Generalised ischaemic cerebrovascular disease NOS
1	40053	G671.00	Generalised ischaemic cerebrovascular disease NOS
1	60188	H320200	Giant bullous emphysema
1	29472	N200.00	Giant cell arteritis with polymyalgia rheumatica
1	19512	C310400	Glycogenosis with hepatic cirrhosis
2	39629	B653100	Granulocytic sarcoma
1	46912	14AM.00	H/O: Heart failure in last year
1	50372	14AH.00	H/O: Myocardial infarction in last year
1	59534	14NB.00	H/O: Peripheral vascular disease procedure
1	16993	14AE.00	H/O: aortic aneurysm
1	719	14B4.00	H/O: asthma
1	41577	1477.00	H/O: cerebrovascular disease
1	5931	1461.00	H/O: dementia
1	6813	1434.00	H/O: diabetes mellitus
1	15058	14A6.00	H/O: heart failure
2	8828	14D1.00	H/O: nephritis
6	51708	A789X00	HIV dis reslt/oth mal neopl/lymph,h'matopoetc+reltd tissu

6	47632	A788U00	HIV disease result/haematological+immunologic abnorms,NEC
6	44617	A789600	HIV disease resulting in Burkitt's lymphoma
6	27853	A789500	HIV disease resulting in Kaposi's sarcoma
6	27641	A789300	HIV disease resulting in Pneumocystis carinii pneumonia
6	23951	A789200	HIV disease resulting in candidiasis
6	66368	A789100	HIV disease resulting in cytomegaloviral disease
6	65117	A789900	HIV disease resulting in lymphoid interstitial pneumonitis
6	50076	A789400	HIV disease resulting in multiple infections
6	105324	A789800	HIV disease resulting in multiple malignant neoplasms
6	37006	A789000	HIV disease resulting in mycobacterial infection
6	67575	A788W00	HIV disease resulting in unspecified malignant neoplasm
6	8281	A789A00	HIV disease resulting in wasting syndrome
6	71450	A788X00	HIV disease resulting/unspcf infectious+parasitic disease
6	69766	A788200	HIV infection with persistent generalised lymphadenopathy
1	29353	N240700	Hand rheumatism
1	5627	H330011	Hay fever with asthma
1	15248	H330.13	Hay fever with asthma
1	16408	G32..11	Healed myocardial infarction
1	1204	G30..14	Heart attack
1	2062	G58..00	Heart failure
1	4024	G58z.00	Heart failure NOS
1	30779	662W.00	Heart failure annual review
1	66306	SP11111	Heart failure as a complication of care
1	32945	8CL3.00	Heart failure care plan discussed with patient

1	9913	1O1..00	Heart failure confirmed
2	63653	B671.11	Heilmeyer - Schoner disease
2	1749	F22..00	Hemiplegia
2	8492	F22z.00	Hemiplegia NOS
3	23511	J622.00	Hepatic coma
1	899	J633.00	Hepatitis unspecified
2	31210	B150100	Hepatoblastoma of liver
2	22187	B150300	Hepatocellular carcinoma
3	10636	J624.00	Hepatorenal syndrome
2	3514	F141.00	Hereditary spastic paraplegia
2	65463	F420800	High risk non proliferative diabetic retinopathy
2	30477	F420700	High risk proliferative diabetic retinopathy
2	108715	B66..11	Histiocytic leukaemia
2	4870	B625.11	Histiocytosis X (acute, progressive)
2	2462	B61..00	Hodgkin's disease
2	42461	B61zz00	Hodgkin's disease NOS
2	53397	B61z.00	Hodgkin's disease NOS
2	107804	B61z300	Hodgkin's disease NOS of intra-abdominal lymph nodes
2	59755	B61z200	Hodgkin's disease NOS of intrathoracic lymph nodes
2	99012	B61z500	Hodgkin's disease NOS of lymph nodes inguinal region and leg
2	91900	B61z400	Hodgkin's disease NOS of lymph nodes of axilla and arm
2	59778	B61z100	Hodgkin's disease NOS of lymph nodes of head, face and neck
2	97746	B61z800	Hodgkin's disease NOS of lymph nodes of multiple sites
2	94279	B61z700	Hodgkin's disease NOS of spleen

2	61662	B61z000	Hodgkin's disease NOS, unspecified site
2	67703	B616.00	Hodgkin's disease, lymphocytic depletion
2	101530	B616z00	Hodgkin's disease, lymphocytic depletion NOS
2	101715	B616700	Hodgkin's disease, lymphocytic depletion of spleen
2	38939	B613.00	Hodgkin's disease, lymphocytic-histiocytic predominance
2	49605	B615.00	Hodgkin's disease, mixed cellularity
2	94005	B615z00	Hodgkin's disease, mixed cellularity NOS
2	97863	B615000	Hodgkin's disease, mixed cellularity of unspecified site
2	29178	B614.00	Hodgkin's disease, nodular sclerosis
2	63054	B614z00	Hodgkin's disease, nodular sclerosis NOS
2	105472	B614700	Hodgkin's disease, nodular sclerosis of spleen
2	57225	B614000	Hodgkin's disease, nodular sclerosis of unspecified site
2	44196	B611.00	Hodgkin's granuloma
2	98909	B611100	Hodgkin's granuloma of lymph nodes of head, face and neck
2	63625	B616400	Hodgkin's lymphocytic depletion lymph nodes axilla and arm
2	110563	B616500	Hodgkin's lymphocytic depletion lymph nodes inguinal and leg
2	107032	B616800	Hodgkin's lymphocytic depletion lymph nodes multiple sites
2	95049	B616000	Hodgkin's lymphocytic depletion of unspecified site
2	58684	B615200	Hodgkin's mixed cellularity of intrathoracic lymph nodes
2	94407	B615100	Hodgkin's mixed cellularity of lymph nodes head, face, neck
2	108886	B615500	Hodgkin's mixed cellularity of lymph nodes inguinal and leg
2	55303	B614100	Hodgkin's nodular sclerosis of head, face and neck
2	61149	B614300	Hodgkin's nodular sclerosis of intra-abdominal lymph nodes
2	67506	B614200	Hodgkin's nodular sclerosis of intrathoracic lymph nodes

2	65483	B614400	Hodgkin's nodular sclerosis of lymph nodes of axilla and arm
2	19140	B614800	Hodgkin's nodular sclerosis of lymph nodes of multiple sites
2	65489	B610.00	Hodgkin's paragranuloma
2	98840	B610300	Hodgkin's paragranuloma of intra-abdominal lymph nodes
2	100423	B610100	Hodgkin's paragranuloma of lymph nodes of head, face, neck
2	64036	B612.00	Hodgkin's sarcoma
2	68039	B612400	Hodgkin's sarcoma of lymph nodes of axilla and upper limb
2	93951	B613500	Hodgkin's, lymphocytic-histiocytic pred inguinal and leg
2	73532	B613300	Hodgkin's, lymphocytic-histiocytic pred intra-abdominal node
2	95338	B613600	Hodgkin's, lymphocytic-histiocytic pred intrapelvic nodes
2	92245	B613200	Hodgkin's, lymphocytic-histiocytic pred intrathoracic nodes
2	68330	B613100	Hodgkin's, lymphocytic-histiocytic pred of head, face, neck
2	104743	B613800	Hodgkin's, lymphocytic-histiocytic pred of multiple sites
2	29876	B613z00	Hodgkin's, lymphocytic-histiocytic predominance NOS
2	106911	B613700	Hodgkin's, lymphocytic-histiocytic predominance of spleen
2	71142	B613000	Hodgkin's, lymphocytic-histiocytic predominance unspec site
6	44303	A789.00	Human immunodef virus resulting in other disease
6	70869	A788300	Human immunodeficiency virus with constitutional disease
6	53636	A788400	Human immunodeficiency virus with neurological disease
6	62891	A788y00	Human immunodeficiency virus with other clinical findings
6	101836	A788600	Human immunodeficiency virus with secondary cancers
6	70528	A788500	Human immunodeficiency virus with secondary infection
2	7978	B4A0000	Hypernephroma
1	36633	C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
1	11833	H35z100	Hypersensitivity pneumonitis NOS

1	21837	G232.00	Hypertensive heart&renal dis wth (congestive) heart failure
2	56939	K08y000	Hypokalaemic nephropathy
1	69124	C107300	IDDM with peripheral circulatory disorder
1	18505	C108.11	IDDM-Insulin dependent diabetes mellitus
2	70716	B62zz11	Immunoproliferative neoplasm
2	43450	B63z.00	Immunoproliferative neoplasm or myeloma NOS
2	6842	K060.11	Impaired renal function
2	25980	K08z.00	Impaired renal function disorder NOS
1	28109	G714100	Inflammatory abdominal aortic aneurysm
1	64446	C108G00	Insulin dependent diab mell with peripheral angiopathy
1	1038	C100011	Insulin dependent diabetes mellitus
1	51261	C10E.12	Insulin dependent diabetes mellitus
1	1647	C108.00	Insulin dependent diabetes mellitus
1	6791	C108800	Insulin dependent diabetes mellitus - poor control
1	72702	C10E812	Insulin dependent diabetes mellitus - poor control
2	65616	C108H00	Insulin dependent diabetes mellitus with arthropathy
2	44260	C108F00	Insulin dependent diabetes mellitus with diabetic cataract
1	60499	C108600	Insulin dependent diabetes mellitus with gangrene
1	44440	C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma
2	24694	C108B00	Insulin dependent diabetes mellitus with mononeuropathy
2	57621	C108D00	Insulin dependent diabetes mellitus with nephropathy
2	41716	C108C00	Insulin dependent diabetes mellitus with polyneuropathy
2	6509	C108700	Insulin dependent diabetes mellitus with retinopathy
1	44443	C108500	Insulin dependent diabetes mellitus with ulcer
1	1407	C10FJ00	Insulin treated Type 2 diabetes mellitus

1	18278	C109J00	Insulin treated Type 2 diabetes mellitus
1	64668	C10FJ11	Insulin treated Type II diabetes mellitus
1	18264	C109J12	Insulin treated Type II diabetes mellitus
1	37648	C109J11	Insulin treated non-insulin dependent diabetes mellitus
2	52283	C108200	Insulin-dependent diabetes mellitus with neurological comps
2	49276	C108100	Insulin-dependent diabetes mellitus with ophthalmic comps
2	46963	C108000	Insulin-dependent diabetes mellitus with renal complications
1	1517	G73z000	Intermittent claudication
1	22905	H581.00	Interstitial emphysema
1	5051	G61..00	Intracerebral haemorrhage
1	3535	G61z.00	Intracerebral haemorrhage NOS
1	31060	G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
1	30202	G617.00	Intracerebral haemorrhage, intraventricular
1	57315	G618.00	Intracerebral haemorrhage, multiple localized
1	20284	G62z.00	Intracranial haemorrhage NOS
1	5267	H331.00	Intrinsic asthma
1	45073	H331z00	Intrinsic asthma NOS
1	18323	H331111	Intrinsic asthma with asthma attack
1	58196	H331100	Intrinsic asthma with status asthmaticus
1	29325	H331000	Intrinsic asthma without status asthmaticus
1	45521	G714000	Juxtarenal aortic aneurysm
2	43552	B630.11	Kahler's disease
2	50290	B6z0.00	Kaposi's sarcoma of lymph nodes
6	65466	B592X00	Kaposi's sarcoma of multiple organs
2	37549	B05z000	Kaposi's sarcoma of palate

2	27931	B33z000	Kaposi's sarcoma of skin
2	104128	B31z000	Kaposi's sarcoma of soft tissue
2	49525	B59zX00	Kaposi's sarcoma, unspecified
2	45499	K01x111	Kimmelstiel - Wilson disease
2	46042	B630300	Lambda light chain myeloma
1	23361	G68..00	Late effects of cerebrovascular disease
1	3665	H331.11	Late onset asthma
1	12987	H33z200	Late-onset asthma
1	14898	G305.00	Lateral myocardial infarction NOS
1	9759	G718.00	Leaking abdominal aortic aneurysm
2	8933	F222.00	Left hemiplegia
1	28314	G61X000	Left sided intracerebral haemorrhage, unspecified
1	884	G581.00	Left ventricular failure
2	34926	B625.00	Letterer-Siwe disease
2	47204	B625z00	Letterer-Siwe disease NOS
2	102158	B625200	Letterer-Siwe disease of intrathoracic lymph nodes
2	54083	B625800	Letterer-Siwe disease of lymph nodes of multiple sites
2	102715	B625000	Letterer-Siwe disease of unspecified sites
2	4250	B68z.00	Leukaemia NOS
2	25191	B68..00	Leukaemia of unspecified cell type
2	65123	B624300	Leukaemic reticuloend of intra-abdominal lymph nodes
2	27330	B624.00	Leukaemic reticuloendotheliosis
2	5137	B624.11	Leukaemic reticuloendotheliosis
2	73777	B624z00	Leukaemic reticuloendotheliosis NOS
2	65122	B624000	Leukaemic reticuloendotheliosis of unspecified sites

1	57675	N000100	Libman-Sacks disease
1	43857	C10M.00	Lipoatrophic diabetes mellitus
3	108800	J62z.00	Liver abscess and chronic liver disease causing sequelae NOS
6	4403	B577.11	Liver metastases
2	2587	B22z.11	Lung cancer
1	34001	H4z..00	Lung disease due to external agents NOS
1	58791	H57y.00	Lung disease with diseases EC
1	63912	H57yz00	Lung disease with diseases EC NOS
1	42940	H57y100	Lung disease with polymyositis
1	31564	H57y400	Lung disease with systemic lupus erythematosus
1	94996	H572.00	Lung disease with systemic sclerosis
1	22205	K01x411	Lupus nephritis
6	7830	B56..11	Lymph node metastases
2	4222	B64..11	Lymphatic leukaemia
2	57737	B62x100	Lymphoepithelioid lymphoma
2	95792	B62zz00	Lymphoid and histiocytic malignancy NOS
2	19372	B64..00	Lymphoid leukaemia
2	38914	B64z.00	Lymphoid leukaemia NOS
2	27416	B601.00	Lymphosarcoma
2	63723	B601z00	Lymphosarcoma NOS
2	41369	B60..00	Lymphosarcoma and reticulosarcoma
2	72197	B67y000	Lymphosarcoma cell leukaemia
2	64670	B601300	Lymphosarcoma of intra-abdominal lymph nodes
2	62380	B601200	Lymphosarcoma of intrathoracic lymph nodes
2	71238	B601100	Lymphosarcoma of lymph nodes of head, face and neck

2 100352 B601500 Lymphosarcoma of lymph nodes of inguinal region and leg

2 104790 B601800 Lymphosarcoma of lymph nodes of multiple sites

2 103245 B601700 Lymphosarcoma of spleen

2 71625 B601000 Lymphosarcoma of unspecified site

1 1677 G30..15 MI - acute myocardial infarction

1 63479 H32y200 MacLeod's unilateral emphysema

1 22841 J615z11 Macronodular cirrhosis of liver

2 106654 B524W00 Mal neoplasm/periph nerves+autonomic nervous system,unspc

2 39531 B25..00 Malig neo, overlapping lesion of heart, mediastinum & pleura

2 24456 B201.00 Malig neop auditory tube, middle ear and mastoid air cells

2 73537 B201z00 Malig neop auditory tube, middle ear, mastoid air cells NOS

2 73718 B310z00 Malig neop connective and soft tissue head, face, neck NOS

2 90546 B312z00 Malig neop connective and soft tissue hip and leg NOS

2 54965 B312200 Malig neop connective and soft tissue of popliteal space

2 65233 B31y.00 Malig neop connective and soft tissue other specified site

2 53989 B311.00 Malig neop connective and soft tissue upper limb/shoulder

2 104913 B311z00 Malig neop connective soft tissue upper limb/shoulder NOS

2 98813 B500.00 Malig neop eyeball excl conjunctiva, cornea, retina, choroid

2 26652 B20..00 Malig neop nasal cavities, middle ear and accessory sinuses

2 18608 B3...00 Malig neop of bone, connective tissue, skin and breast

2 41011 B3z..00 Malig neop of bone, connective tissue, skin and breast NOS

2 19389 B3y..00 Malig neop of bone, connective tissue, skin and breast OS

2 43475 B310.00 Malig neop of connective and soft tissue head, face and neck

2 60247 B314z00 Malig neop of connective and soft tissue of abdomen NOS

2	66488	B314000	Malig neop of connective and soft tissue of abdominal wall
2	66088	B312.00	Malig neop of connective and soft tissue of hip and leg
2	67324	B315100	Malig neop of connective and soft tissue of inguinal region
2	30542	B312300	Malig neop of connective and soft tissue of lower leg
2	58836	B315z00	Malig neop of connective and soft tissue of pelvis NOS
2	98408	B313z00	Malig neop of connective and soft tissue of thorax NOS
2	44805	B312100	Malig neop of connective and soft tissue thigh and upper leg
2	57471	B316.00	Malig neop of connective and soft tissue trunk unspecified
2	64195	B54z.00	Malig neop of endocrine gland or related structure NOS
2	13559	B4A..00	Malig neop of kidney and other unspecified urinary organs
2	4555	B45..00	Malig neop of other and unspecified female genital organs
2	65458	B52..00	Malig neop of other and unspecified parts of nervous system
2	30511	B54..00	Malig neop of other endocrine glands and related structures
2	100232	B24y.00	Malig neop of other site of heart, thymus and mediastinum
2	34075	B2...00	Malig neop of respiratory tract and intrathoracic organs
2	65880	B304z00	Malig neop of scapula and long bones of upper arm NOS
2	65793	B2z0.00	Malig neop of upper respiratory tract, part unspecified
2	11009	B1z..00	Malig neop oth/ill-defined sites digestive tract/peritoneum
2	96971	B20y.00	Malig neop other site nasal cavity, middle ear and sinuses
2	55659	B14y.00	Malig neop other site rectum, rectosigmoid junction and anus
2	46114	B0z..00	Malig neop other/ill-defined sites lip, oral cavity, pharynx
2	44356	B2z..00	Malig neop other/ill-defined sites resp/intrathoracic organs
2	59718	B542z00	Malig neop pituitary gland or craniopharyngeal duct NOS
2	62399	B332z00	Malig neop skin of ear and external auricular canal NOS
2	110192	B315300	Malig neopl of connective and soft tissue - sacrum or coccyx

2	24235	B524.00	Malig neopl peripheral nerves and autonomic nervous system
2	53504	B52W.00	Malig neopl, overlap lesion brain & other part of CNS
2	94272	B314100	Malig neoplasm of connective and soft tissues of lumb spine
2	104139	B313300	Malig neoplasm of connective and soft tissues of thor spine
6	8154	B576200	Malignant ascites
2	44267	B623.00	Malignant histiocytosis
2	58871	B623z00	Malignant histiocytosis NOS
2	65642	B623300	Malignant histiocytosis of intra-abdominal lymph nodes
2	94415	B623100	Malignant histiocytosis of lymph nodes head, face and neck
2	110903	B623800	Malignant histiocytosis of lymph nodes of multiple sites
2	69497	B623000	Malignant histiocytosis of unspecified site
2	58962	B62x500	Malignant immunoproliferative small intestinal disease
2	15027	B62yz00	Malignant lymphoma NOS
2	12335	B62y.00	Malignant lymphoma NOS
2	42579	B62y300	Malignant lymphoma NOS of intra-abdominal lymph nodes
2	71262	B62y600	Malignant lymphoma NOS of intrapelvic lymph nodes
2	72725	B62y200	Malignant lymphoma NOS of intrathoracic lymph nodes
2	63105	B62y500	Malignant lymphoma NOS of lymph node inguinal region and leg
2	34089	B62y400	Malignant lymphoma NOS of lymph nodes of axilla and arm
2	50696	B62y100	Malignant lymphoma NOS of lymph nodes of head, face and neck
2	15504	B62y800	Malignant lymphoma NOS of lymph nodes of multiple sites
2	60092	B62y700	Malignant lymphoma NOS of spleen
2	57427	B62y000	Malignant lymphoma NOS of unspecified site
2	17887	B62x.00	Malignant lymphoma otherwise specified

2	89657	B626z00	Malignant mast cell tumour NOS
2	15036	B626.00	Malignant mast cell tumours
2	42714	B327500	Malignant melanoma of ankle
2	59061	B322000	Malignant melanoma of auricle (ear)
2	49814	B325000	Malignant melanoma of axilla
2	43463	B325700	Malignant melanoma of back
2	32768	B325100	Malignant melanoma of breast
2	53629	B325200	Malignant melanoma of buttock
2	51209	B325800	Malignant melanoma of chest wall
2	71136	B323100	Malignant melanoma of chin
2	57260	B322.00	Malignant melanoma of ear and external auricular canal
2	73744	B322z00	Malignant melanoma of ear and external auricular canal NOS
2	102145	B322100	Malignant melanoma of external auditory meatus
2	41278	B323000	Malignant melanoma of external surface of cheek
2	45139	B323400	Malignant melanoma of external surface of nose
2	47094	B323200	Malignant melanoma of eyebrow
2	54632	B321.00	Malignant melanoma of eyelid including canthus
2	67806	B323z00	Malignant melanoma of face NOS
2	25602	B326400	Malignant melanoma of finger
2	41490	B327700	Malignant melanoma of foot
2	45755	B326200	Malignant melanoma of fore-arm
2	68133	B323300	Malignant melanoma of forehead
2	53369	B327900	Malignant melanoma of great toe
2	34259	B325300	Malignant melanoma of groin
2	62475	B326300	Malignant melanoma of hand

2	61246	B327600	Malignant melanoma of heel
2	73536	B327000	Malignant melanoma of hip
2	54305	B327200	Malignant melanoma of knee
2	70637	B320.00	Malignant melanoma of lip
2	37872	B327400	Malignant melanoma of lower leg
2	46255	B327.00	Malignant melanoma of lower limb and hip
2	64327	B327z00	Malignant melanoma of lower limb or hip NOS
2	45306	B324100	Malignant melanoma of neck
2	47252	B323.00	Malignant melanoma of other and unspecified parts of face
2	42153	B32y.00	Malignant melanoma of other specified skin site
2	109002	B325400	Malignant melanoma of perianal skin
2	95629	B325500	Malignant melanoma of perineum
2	39878	B327300	Malignant melanoma of popliteal fossa area
2	55881	B324000	Malignant melanoma of scalp
2	65625	B324.00	Malignant melanoma of scalp and neck
2	99257	B324z00	Malignant melanoma of scalp and neck NOS
2	50505	B326000	Malignant melanoma of shoulder
2	865	B32..00	Malignant melanoma of skin
2	28556	B32z.00	Malignant melanoma of skin NOS
2	58958	B323500	Malignant melanoma of temple
2	51873	B327100	Malignant melanoma of thigh
2	63997	B326500	Malignant melanoma of thumb
2	36899	B327800	Malignant melanoma of toe
2	38689	B325.00	Malignant melanoma of trunk (excluding scrotum)
2	45760	B325z00	Malignant melanoma of trunk, excluding scrotum, NOS

2	43715	B325600	Malignant melanoma of umbilicus
2	54685	B326100	Malignant melanoma of upper arm
2	65164	B326.00	Malignant melanoma of upper limb and shoulder
2	55292	B326z00	Malignant melanoma of upper limb or shoulder NOS
2	57248	B082.00	Malignant neoplasm aryepiglottic fold, hypopharyngeal aspect
2	15711	B510.00	Malignant neoplasm cerebrum (excluding lobes and ventricles)
2	54103	B16..00	Malignant neoplasm gallbladder and extrahepatic bile ducts
2	15907	B16z.00	Malignant neoplasm gallbladder/extrahepatic bile ducts NOS
2	49301	B6z..00	Malignant neoplasm lymphatic or haematopoietic tissue NOS
2	30646	B6y..00	Malignant neoplasm lymphatic or haematopoietic tissue OS
2	35795	B174.00	Malignant neoplasm of Islets of Langerhans
2	63995	B123.00	Malignant neoplasm of Meckel's diverticulum
2	95016	B0z1.00	Malignant neoplasm of Waldeyer's ring
2	15976	B552.00	Malignant neoplasm of abdomen
2	63470	B102.00	Malignant neoplasm of abdominal oesophagus
2	55246	B20z.00	Malignant neoplasm of accessory sinus NOS
2	65599	B520200	Malignant neoplasm of acoustic nerve
2	105797	B304100	Malignant neoplasm of acromion
2	33388	B071000	Malignant neoplasm of adenoid
2	61390	B540000	Malignant neoplasm of adrenal cortex
2	28148	B540.00	Malignant neoplasm of adrenal gland
2	70824	B540z00	Malignant neoplasm of adrenal gland NOS
2	94220	B540100	Malignant neoplasm of adrenal medulla
2	10949	B162.00	Malignant neoplasm of ampulla of Vater
2	24370	B142.00	Malignant neoplasm of anal canal

2	58121	B014.00	Malignant neoplasm of anterior 2/3 of tongue unspecified
2	102142	B013000	Malignant neoplasm of anterior 2/3 of tongue ventral surface
2	46728	B064.00	Malignant neoplasm of anterior epiglottis
2	73439	B064z00	Malignant neoplasm of anterior epiglottis NOS
2	27715	B242.00	Malignant neoplasm of anterior mediastinum
2	45408	B040.00	Malignant neoplasm of anterior portion of floor of mouth
2	44139	B073.00	Malignant neoplasm of anterior wall of nasopharynx
2	100918	B073z00	Malignant neoplasm of anterior wall of nasopharynx NOS
2	65312	B11y000	Malignant neoplasm of anterior wall of stomach NEC
2	19162	B493.00	Malignant neoplasm of anterior wall of urinary bladder
2	27897	B143.00	Malignant neoplasm of anus unspecified
2	47840	B545100	Malignant neoplasm of aortic body
2	50035	B545.00	Malignant neoplasm of aortic body and other paraganglia
2	103995	B545z00	Malignant neoplasm of aortic body or paraganglia NOS
2	18632	B135.00	Malignant neoplasm of appendix
2	64686	B340100	Malignant neoplasm of areola of female breast
2	67884	B350100	Malignant neoplasm of areola of male breast
2	63460	B213000	Malignant neoplasm of arytenoid cartilage
2	10946	B136.00	Malignant neoplasm of ascending colon
2	107916	B201000	Malignant neoplasm of auditory (Eustachian) tube
2	37618	B551000	Malignant neoplasm of axilla NOS
2	20685	B346.00	Malignant neoplasm of axillary tail of female breast
2	68787	B55y000	Malignant neoplasm of back NOS
2	48073	B510000	Malignant neoplasm of basal ganglia
2	43431	B010.00	Malignant neoplasm of base of tongue

2	34409	B010000	Malignant neoplasm of base of tongue dorsal surface
2	41571	B495.00	Malignant neoplasm of bladder neck
2	40810	B171.00	Malignant neoplasm of body of pancreas
2	48743	B482.00	Malignant neoplasm of body of penis
2	43572	B114.00	Malignant neoplasm of body of stomach
2	7046	B43..00	Malignant neoplasm of body of uterus
2	33617	B43z.00	Malignant neoplasm of body of uterus NOS
2	18314	B30..00	Malignant neoplasm of bone and articular cartilage
2	16075	B30z.00	Malignant neoplasm of bone and articular cartilage NOS
2	59036	B300.00	Malignant neoplasm of bones of skull and face
2	69146	B300z00	Malignant neoplasm of bones of skull and face NOS
2	18617	B51..00	Malignant neoplasm of brain
2	41520	B51z.00	Malignant neoplasm of brain NOS
2	44089	B517.00	Malignant neoplasm of brain stem
2	68641	B517z00	Malignant neoplasm of brain stem NOS
2	101778	B442.00	Malignant neoplasm of broad ligament
2	3903	B22z.00	Malignant neoplasm of bronchus or lung NOS
2	30402	B050.11	Malignant neoplasm of buccal mucosa
2	3811	B134.00	Malignant neoplasm of caecum
2	72212	B308200	Malignant neoplasm of calcaneum
2	36731	B331000	Malignant neoplasm of canthus
2	32022	B110.00	Malignant neoplasm of cardia of stomach
2	37859	B110z00	Malignant neoplasm of cardia of stomach NOS
2	100584	B110000	Malignant neoplasm of cardiac orifice of stomach
2	22894	B110100	Malignant neoplasm of cardio-oesophageal junction of

stomach

2	17391	B221000	Malignant neoplasm of carina of bronchus
2	57047	B544.00	Malignant neoplasm of carotid body
2	69104	B305100	Malignant neoplasm of carpal bone - lunate
2	57988	B305000	Malignant neoplasm of carpal bone - scaphoid
2	106069	B305.11	Malignant neoplasm of carpal bones
2	60035	B310300	Malignant neoplasm of cartilage of ear
2	71204	B200000	Malignant neoplasm of cartilage of nose
2	9622	B525.00	Malignant neoplasm of cauda equina
2	31546	B341.00	Malignant neoplasm of central part of female breast
2	45154	B516.00	Malignant neoplasm of cerebellum
2	61399	B510100	Malignant neoplasm of cerebral cortex
2	110766	B521000	Malignant neoplasm of cerebral dura mater
2	28919	B521.00	Malignant neoplasm of cerebral meninges
2	70104	B521z00	Malignant neoplasm of cerebral meninges NOS
2	64557	B517000	Malignant neoplasm of cerebral peduncle
2	109473	B521200	Malignant neoplasm of cerebral pia mater
2	52511	B515.00	Malignant neoplasm of cerebral ventricles
2	54133	B510z00	Malignant neoplasm of cerebrum NOS
2	61695	B100.00	Malignant neoplasm of cervical oesophagus
2	95505	B41y000	Malignant neoplasm of cervical stump
2	46939	B302000	Malignant neoplasm of cervical vertebra
2	2747	B41..00	Malignant neoplasm of cervix uteri
2	28311	B41z.00	Malignant neoplasm of cervix uteri NOS
2	41931	B550100	Malignant neoplasm of cheek NOS

2	31364	B050.00	Malignant neoplasm of cheek mucosa
2	23861	B551100	Malignant neoplasm of chest wall NOS
2	15991	B506.00	Malignant neoplasm of choroid
2	46789	B515000	Malignant neoplasm of choroid plexus
2	59041	B500000	Malignant neoplasm of ciliary body
2	66639	B303200	Malignant neoplasm of clavicle
2	53910	B453.00	Malignant neoplasm of clitoris
2	46159	B142000	Malignant neoplasm of cloacogenic zone
2	46905	B545200	Malignant neoplasm of coccygeal body
2	66908	B306400	Malignant neoplasm of coccygeal vertebra
2	1220	B13..00	Malignant neoplasm of colon
2	28163	B13z.00	Malignant neoplasm of colon NOS
2	96783	B005.00	Malignant neoplasm of commissure of lip
2	7982	B161200	Malignant neoplasm of common bile duct
2	63657	B503.00	Malignant neoplasm of conjunctiva
2	34451	B31..00	Malignant neoplasm of connective and other soft tissue
2	45071	B314.00	Malignant neoplasm of connective and soft tissue of abdomen
2	29160	B313000	Malignant neoplasm of connective and soft tissue of axilla
2	70463	B315000	Malignant neoplasm of connective and soft tissue of buttock
2	91586	B311400	Malignant neoplasm of connective and soft tissue of finger
2	54222	B312400	Malignant neoplasm of connective and soft tissue of foot
2	57482	B311200	Malignant neoplasm of connective and soft tissue of fore-arm
2	19321	B311300	Malignant neoplasm of connective and soft tissue of hand
2	102949	B312000	Malignant neoplasm of connective and soft tissue of hip
2	51965	B315.00	Malignant neoplasm of connective and soft tissue of pelvis

2	59152	B315200	Malignant neoplasm of connective and soft tissue of perineum
2	50222	B311000	Malignant neoplasm of connective and soft tissue of shoulder
2	22290	B313.00	Malignant neoplasm of connective and soft tissue of thorax
2	63988	B311500	Malignant neoplasm of connective and soft tissue of thumb
2	99572	B312500	Malignant neoplasm of connective and soft tissue of toe
2	15182	B31z.00	Malignant neoplasm of connective and soft tissue, site NOS
2	64345	B311100	Malignant neoplasm of connective and soft tissue, upper arm
2	86996	B501000	Malignant neoplasm of connective tissue of orbit
2	73992	B504.00	Malignant neoplasm of cornea
2	72723	B430000	Malignant neoplasm of cornu of corpus uteri
2	59170	B51y000	Malignant neoplasm of corpus callosum
2	45490	B430z00	Malignant neoplasm of corpus uteri NOS
2	3213	B430.00	Malignant neoplasm of corpus uteri, excluding isthmus
2	60403	B303300	Malignant neoplasm of costal cartilage
2	67763	B303400	Malignant neoplasm of costo-vertebral joint
2	99621	B520.00	Malignant neoplasm of cranial nerves
2	101086	B520z00	Malignant neoplasm of cranial nerves NOS
2	39899	B542100	Malignant neoplasm of craniopharyngeal duct
2	37805	B213100	Malignant neoplasm of cricoid cartilage
2	106569	B500200	Malignant neoplasm of crystalline lens
2	107878	B213200	Malignant neoplasm of cuneiform cartilage
2	72445	B161000	Malignant neoplasm of cystic duct
2	19475	B471.00	Malignant neoplasm of descended testis
2	10864	B132.00	Malignant neoplasm of descending colon
2	54186	B313100	Malignant neoplasm of diaphragm

2	15709	B1...00	Malignant neoplasm of digestive organs and peritoneum
2	51255	B1zz.00	Malignant neoplasm of digestive tract and peritoneum NOS
2	44996	B491.00	Malignant neoplasm of dome of urinary bladder
2	43642	B011.00	Malignant neoplasm of dorsal surface of tongue
2	43781	B011z00	Malignant neoplasm of dorsum of tongue NOS
2	18613	B120.00	Malignant neoplasm of duodenum
2	96635	B17y000	Malignant neoplasm of ectopic pancreatic tissue
2	95057	B34y000	Malignant neoplasm of ectopic site of female breast
2	95323	B35z000	Malignant neoplasm of ectopic site of male breast
2	63430	B241000	Malignant neoplasm of endocardium
2	57235	B410000	Malignant neoplasm of endocervical canal
2	53103	B410100	Malignant neoplasm of endocervical gland
2	48820	B410.00	Malignant neoplasm of endocervix
2	50285	B410z00	Malignant neoplasm of endocervix NOS
2	49400	B430211	Malignant neoplasm of endometrium
2	2890	B430200	Malignant neoplasm of endometrium of corpus uteri
2	72127	B484.00	Malignant neoplasm of epididymis
2	55374	B215.00	Malignant neoplasm of epiglottis NOS
2	26134	B064000	Malignant neoplasm of epiglottis, free border
2	53594	B300000	Malignant neoplasm of ethmoid bone
2	54636	B203.00	Malignant neoplasm of ethmoid sinus
2	50297	B411.00	Malignant neoplasm of exocervix
2	23433	B161.00	Malignant neoplasm of extrahepatic bile ducts
2	74896	B161z00	Malignant neoplasm of extrahepatic bile ducts NOS
2	20160	B50..00	Malignant neoplasm of eye

2	54956	B50z.00	Malignant neoplasm of eye NOS
2	56718	B500z00	Malignant neoplasm of eyeball NOS
2	43087	B331.00	Malignant neoplasm of eyelid including canthus
2	49828	B441.00	Malignant neoplasm of fallopian tube
2	51926	B062000	Malignant neoplasm of faucial pillar
2	26448	B060000	Malignant neoplasm of faucial tonsil
2	3968	B34..00	Malignant neoplasm of female breast
2	9470	B34z.00	Malignant neoplasm of female breast NOS
2	20166	B45z.00	Malignant neoplasm of female genital organ NOS
2	56513	B307000	Malignant neoplasm of femur
2	50402	B307100	Malignant neoplasm of fibula
2	94427	B305C00	Malignant neoplasm of fifth metacarpal bone
2	110993	B305800	Malignant neoplasm of first metacarpal bone
2	69927	B308800	Malignant neoplasm of first metatarsal bone
2	91035	B010z00	Malignant neoplasm of fixed part of tongue NOS
2	94355	B55y200	Malignant neoplasm of flank NOS
2	20092	B04..00	Malignant neoplasm of floor of mouth
2	36716	B04z.00	Malignant neoplasm of floor of mouth NOS
2	63979	B013100	Malignant neoplasm of frenulum linguae
2	53599	B300100	Malignant neoplasm of frontal bone
2	42426	B511.00	Malignant neoplasm of frontal lobe
2	15684	B204.00	Malignant neoplasm of frontal sinus
2	68155	B430100	Malignant neoplasm of fundus of corpus uteri
2	32362	B113.00	Malignant neoplasm of fundus of stomach
2	16105	B160.00	Malignant neoplasm of gallbladder

2	94278	B110111	Malignant neoplasm of gastro-oesophageal junction
2	13252	B4...00	Malignant neoplasm of genitourinary organ
2	52594	B4z..00	Malignant neoplasm of genitourinary organ NOS
2	38931	B4y..00	Malignant neoplasm of genitourinary organ OS
2	17841	B481.00	Malignant neoplasm of glans penis
2	99913	B510300	Malignant neoplasm of globus pallidus
2	51795	B545000	Malignant neoplasm of glomus jugulare
2	91895	B064100	Malignant neoplasm of glossoepiglottic fold
2	99185	B062100	Malignant neoplasm of glossopalatine fold
2	318	B210.00	Malignant neoplasm of glottis
2	72522	B313200	Malignant neoplasm of great vessels
2	55434	B116.00	Malignant neoplasm of greater curve of stomach unspecified
2	47899	B451000	Malignant neoplasm of greater vestibular (Bartholin's) gland
2	43400	B03..00	Malignant neoplasm of gum
2	93218	B03z.00	Malignant neoplasm of gum NOS
2	73530	B305.00	Malignant neoplasm of hand bones
2	73556	B305z00	Malignant neoplasm of hand bones NOS
2	37590	B052.00	Malignant neoplasm of hard palate
2	55098	B550000	Malignant neoplasm of head NOS
2	8771	B170.00	Malignant neoplasm of head of pancreas
2	68236	B550.00	Malignant neoplasm of head, neck and face
2	58903	B550z00	Malignant neoplasm of head, neck and face NOS
2	95644	B241.00	Malignant neoplasm of heart
2	50289	B241z00	Malignant neoplasm of heart NOS
2	66750	B24z.00	Malignant neoplasm of heart, thymus and mediastinum NOS

2	52537	B161100	Malignant neoplasm of hepatic duct
2	9088	B130.00	Malignant neoplasm of hepatic flexure of colon
2	33444	B221100	Malignant neoplasm of hilus of lung
2	67236	B512000	Malignant neoplasm of hippocampus
2	37112	B6...11	Malignant neoplasm of histiocytic tissue
2	61741	B304200	Malignant neoplasm of humerus
2	34012	B08..00	Malignant neoplasm of hypopharynx
2	28451	B08z.00	Malignant neoplasm of hypopharynx NOS
2	70942	B510400	Malignant neoplasm of hypothalamus
2	33871	B122.00	Malignant neoplasm of ileum
2	44609	B306000	Malignant neoplasm of ilium
2	57854	B553000	Malignant neoplasm of inguinal region NOS
2	65124	B151000	Malignant neoplasm of interlobular bile ducts
2	110775	B151100	Malignant neoplasm of interlobular biliary canals
2	17559	B1z0.00	Malignant neoplasm of intestinal tract, part unspecified
2	16915	B151.00	Malignant neoplasm of intrahepatic bile ducts
2	61643	B151z00	Malignant neoplasm of intrahepatic bile ducts NOS
2	89593	B151200	Malignant neoplasm of intrahepatic biliary passages
2	58088	B151400	Malignant neoplasm of intrahepatic gall duct
2	97547	B551200	Malignant neoplasm of intrathoracic site NOS
2	59381	B500100	Malignant neoplasm of iris
2	59223	B306100	Malignant neoplasm of ischium
2	43940	B431.00	Malignant neoplasm of isthmus of uterine body
2	70729	B431z00	Malignant neoplasm of isthmus of uterine body NOS
2	51818	B550300	Malignant neoplasm of jaw NOS

2	43479	B121.00	Malignant neoplasm of jejunum
2	96003	B055000	Malignant neoplasm of junction of hard and soft palate
2	48519	B065.00	Malignant neoplasm of junctional region of epiglottis
2	29462	B4Az.00	Malignant neoplasm of kidney or urinary organs NOS
2	1599	B4A0.00	Malignant neoplasm of kidney parenchyma
2	43761	B451.00	Malignant neoplasm of labia majora
2	59362	B451z00	Malignant neoplasm of labia majora NOS
2	58061	B452.00	Malignant neoplasm of labia minora
2	71584	B507.00	Malignant neoplasm of lacrimal duct
2	64817	B502.00	Malignant neoplasm of lacrimal gland
2	101805	B507000	Malignant neoplasm of lacrimal sac
2	43111	B213.00	Malignant neoplasm of laryngeal cartilage
2	97332	B213z00	Malignant neoplasm of laryngeal cartilage NOS
2	39084	B0z2.00	Malignant neoplasm of laryngopharynx
2	319	B21..00	Malignant neoplasm of larynx
2	9237	B21z.00	Malignant neoplasm of larynx NOS
2	26813	B21y.00	Malignant neoplasm of larynx, other specified site
2	45986	B041.00	Malignant neoplasm of lateral portion of floor of mouth
2	59004	B072.00	Malignant neoplasm of lateral wall of nasopharynx
2	102205	B072z00	Malignant neoplasm of lateral wall of nasopharynx NOS
2	56355	B066.00	Malignant neoplasm of lateral wall of oropharynx
2	35963	B492.00	Malignant neoplasm of lateral wall of urinary bladder
2	42193	B115.00	Malignant neoplasm of lesser curve of stomach unspecified
2	24852	B016.00	Malignant neoplasm of lingual tonsil
2	14712	B00..00	Malignant neoplasm of lip

2	73614	B004000	Malignant neoplasm of lip unspecified, buccal aspect
2	61692	B004.00	Malignant neoplasm of lip unspecified, inner aspect
2	68399	B004200	Malignant neoplasm of lip unspecified, mucosa
2	100144	B004300	Malignant neoplasm of lip, oral aspect
2	19415	B0...00	Malignant neoplasm of lip, oral cavity and pharynx
2	39430	B0zz.00	Malignant neoplasm of lip, oral cavity and pharynx NOS
2	37553	B007.00	Malignant neoplasm of lip, unspecified
2	100906	B00z000	Malignant neoplasm of lip, unspecified, external
2	94251	B00z100	Malignant neoplasm of lip, unspecified, lipstick area
2	69761	B00zz00	Malignant neoplasm of lip, vermilion border NOS
2	8918	B15..00	Malignant neoplasm of liver and intrahepatic bile ducts
2	38978	B15z.00	Malignant neoplasm of liver and intrahepatic bile ducts NOS
2	26393	B152.00	Malignant neoplasm of liver unspecified
2	68055	B307.00	Malignant neoplasm of long bones of leg
2	62630	B307z00	Malignant neoplasm of long bones of leg NOS
2	97530	B051100	Malignant neoplasm of lower buccal sulcus
2	41958	B331200	Malignant neoplasm of lower eyelid
2	49360	B031.00	Malignant neoplasm of lower gum
2	31399	B555.00	Malignant neoplasm of lower limb NOS
2	67504	B003000	Malignant neoplasm of lower lip, buccal aspect
2	66384	B001000	Malignant neoplasm of lower lip, external
2	91843	B003100	Malignant neoplasm of lower lip, frenulum
2	71147	B003.00	Malignant neoplasm of lower lip, inner aspect
2	96782	B003z00	Malignant neoplasm of lower lip, inner aspect NOS
2	95480	B001100	Malignant neoplasm of lower lip, lipstick area

2	89909	B003200	Malignant neoplasm of lower lip, mucosa
2	94441	B003300	Malignant neoplasm of lower lip, oral aspect
2	67446	B001.00	Malignant neoplasm of lower lip, vermilion border
2	101707	B001z00	Malignant neoplasm of lower lip, vermilion border NOS
2	18678	B224000	Malignant neoplasm of lower lobe bronchus
2	12582	B224100	Malignant neoplasm of lower lobe of lung
2	31188	B224.00	Malignant neoplasm of lower lobe, bronchus or lung
2	42566	B224z00	Malignant neoplasm of lower lobe, bronchus or lung NOS
2	42416	B105.00	Malignant neoplasm of lower third of oesophagus
2	59097	B431000	Malignant neoplasm of lower uterine segment
2	45222	B343.00	Malignant neoplasm of lower-inner quadrant of female breast
2	42070	B345.00	Malignant neoplasm of lower-outer quadrant of female breast
2	54691	B302200	Malignant neoplasm of lumbar vertebra
2	12323	B6...00	Malignant neoplasm of lymphatic and haemopoietic tissue
2	12870	B221.00	Malignant neoplasm of main bronchus
2	21698	B221z00	Malignant neoplasm of main bronchus NOS
2	50475	B02z.00	Malignant neoplasm of major salivary gland NOS
2	20292	B02..00	Malignant neoplasm of major salivary glands
2	59520	B300200	Malignant neoplasm of malar bone
2	19423	B35..00	Malignant neoplasm of male breast
2	48809	B35zz00	Malignant neoplasm of male breast NOS
2	33833	B301.00	Malignant neoplasm of mandible
2	71946	B201300	Malignant neoplasm of mastoid air cells
2	17475	B300A00	Malignant neoplasm of maxilla
2	32174	B202.00	Malignant neoplasm of maxillary sinus

2	34878	B308300	Malignant neoplasm of medial cuneiform
2	61064	B24X.00	Malignant neoplasm of mediastinum, part unspecified
2	49132	B517100	Malignant neoplasm of medulla oblongata
2	49875	B52X.00	Malignant neoplasm of meninges, unspecified
2	90290	B18y700	Malignant neoplasm of mesentery
2	59388	B18y100	Malignant neoplasm of mesocaecum
2	30165	B18y200	Malignant neoplasm of mesorectum
2	72464	B305.12	Malignant neoplasm of metacarpal bones
2	93537	B517200	Malignant neoplasm of midbrain
2	41523	B223000	Malignant neoplasm of middle lobe bronchus
2	39923	B223100	Malignant neoplasm of middle lobe of lung
2	31268	B223.00	Malignant neoplasm of middle lobe, bronchus or lung
2	54134	B223z00	Malignant neoplasm of middle lobe, bronchus or lung NOS
2	54171	B104.00	Malignant neoplasm of middle third of oesophagus
2	107258	B011100	Malignant neoplasm of midline of tongue
2	55015	B05z.00	Malignant neoplasm of mouth NOS
2	103946	B220100	Malignant neoplasm of mucosa of trachea
2	65605	B241200	Malignant neoplasm of myocardium
2	45793	B430300	Malignant neoplasm of myometrium of corpus uteri
2	95458	B300300	Malignant neoplasm of nasal bone
2	23389	B200.00	Malignant neoplasm of nasal cavities
2	42856	B200z00	Malignant neoplasm of nasal cavities NOS
2	98911	B200100	Malignant neoplasm of nasal conchae
2	65357	B507100	Malignant neoplasm of nasolacrimal duct
2	106915	B073100	Malignant neoplasm of nasopharyngeal soft palate surface

2	24675	B07..00	Malignant neoplasm of nasopharynx
2	28665	B07z.00	Malignant neoplasm of nasopharynx NOS
2	16280	B550400	Malignant neoplasm of neck NOS
2	56490	B52z.00	Malignant neoplasm of nervous system NOS
2	26853	B340.00	Malignant neoplasm of nipple and areola of female breast
2	54494	B350.00	Malignant neoplasm of nipple and areola of male breast
2	23380	B340000	Malignant neoplasm of nipple of female breast
2	68480	B350000	Malignant neoplasm of nipple of male breast
2	59831	B340z00	Malignant neoplasm of nipple or areola of female breast NOS
2	12490	B550200	Malignant neoplasm of nose NOS
2	55953	B300400	Malignant neoplasm of occipital bone
2	39088	B514.00	Malignant neoplasm of occipital lobe
2	1062	B10..00	Malignant neoplasm of oesophagus
2	30700	B10z.00	Malignant neoplasm of oesophagus NOS
2	64971	B520000	Malignant neoplasm of olfactory bulb
2	50898	B18y300	Malignant neoplasm of omentum
2	70126	B520100	Malignant neoplasm of optic nerve
2	45667	B501.00	Malignant neoplasm of orbit
2	63104	B501z00	Malignant neoplasm of orbit NOS
2	50298	B300500	Malignant neoplasm of orbital bone
2	22893	B06..00	Malignant neoplasm of oropharynx
2	43200	B06z.00	Malignant neoplasm of oropharynx NOS
2	67323	B06y.00	Malignant neoplasm of oropharynx, other specified sites
2	45267	B55z.00	Malignant neoplasm of other and ill defined site NOS
2	9030	B55..00	Malignant neoplasm of other and ill-defined sites

2	14792	B05..00	Malignant neoplasm of other and unspecified parts of mouth
6	1056	B5z..00	Malignant neoplasm of other and unspecified site NOS
6	38736	B5y..00	Malignant neoplasm of other and unspecified site OS
2	10995	B5...00	Malignant neoplasm of other and unspecified sites
2	70696	B02y.00	Malignant neoplasm of other major salivary glands
2	67949	B48y.00	Malignant neoplasm of other male genital organ
2	92329	B48yz00	Malignant neoplasm of other male genital organ NOS
2	100733	B51yz00	Malignant neoplasm of other part of brain NOS
2	71139	B51y.00	Malignant neoplasm of other parts of brain
2	32955	B41y.00	Malignant neoplasm of other site of cervix
2	43435	B41yz00	Malignant neoplasm of other site of cervix NOS
2	56715	B34y.00	Malignant neoplasm of other site of female breast
2	38475	B34yz00	Malignant neoplasm of other site of female breast NOS
2	54202	B35z.00	Malignant neoplasm of other site of male breast
2	29283	B2zy.00	Malignant neoplasm of other site of respiratory tract
2	36949	B49y.00	Malignant neoplasm of other site of urinary bladder
2	97996	B44y.00	Malignant neoplasm of other site of uterine adnexa
2	31608	B43y.00	Malignant neoplasm of other site of uterine body
2	49758	B0zy.00	Malignant neoplasm of other sites lip, oral cavity, pharynx
2	38961	B22y.00	Malignant neoplasm of other sites of bronchus or lung
2	56709	B04y.00	Malignant neoplasm of other sites of floor of mouth
2	101753	B03y.00	Malignant neoplasm of other sites of gum
2	41530	B01y.00	Malignant neoplasm of other sites of tongue
2	90659	B54y.00	Malignant neoplasm of other specified endocrine gland
2	95421	B45y.00	Malignant neoplasm of other specified female genital organ

2	88362	B08y.00	Malignant neoplasm of other specified hypopharyngeal site
2	37916	B05y.00	Malignant neoplasm of other specified mouth parts
2	88144	B52y.00	Malignant neoplasm of other specified part of nervous system
2	53591	B10y.00	Malignant neoplasm of other specified part of oesophagus
2	98104	B23y.00	Malignant neoplasm of other specified pleura
2	40437	B50y.00	Malignant neoplasm of other specified site of eye
2	55630	B07y.00	Malignant neoplasm of other specified site of nasopharynx
2	91037	B06yz00	Malignant neoplasm of other specified site of oropharynx NOS
2	55019	B11y.00	Malignant neoplasm of other specified site of stomach
2	65372	B11yz00	Malignant neoplasm of other specified site of stomach NOS
2	99896	B12y.00	Malignant neoplasm of other specified site small intestine
2	42218	B55y.00	Malignant neoplasm of other specified sites
2	48231	B13y.00	Malignant neoplasm of other specified sites of colon
2	48537	B17y.00	Malignant neoplasm of other specified sites of pancreas
2	18354	B33y.00	Malignant neoplasm of other specified skin sites
2	44884	B4Ay.00	Malignant neoplasm of other urinary organs
2	7805	B440.00	Malignant neoplasm of ovary
2	19141	B44..00	Malignant neoplasm of ovary and other uterine adnexa
2	36371	B225.00	Malignant neoplasm of overlapping lesion of bronchus & lung
2	16967	B432.00	Malignant neoplasm of overlapping lesion of corpus uteri
2	18882	B006.00	Malignant neoplasm of overlapping lesion of lip
2	102151	B060200	Malignant neoplasm of overlapping lesion of tonsil
2	59286	B4Ay000	Malignant neoplasm of overlapping lesion of urinary organs
2	27617	B45y000	Malignant neoplasm of overlapping lesion of vulva

2 28559 B055z00 Malignant neoplasm of palate NOS

2 70819 B055.00 Malignant neoplasm of palate unspecified

2 101988 B060100 Malignant neoplasm of palatine tonsil

2 61510 B062200 Malignant neoplasm of palatoglossal arch

2 93842 B062300 Malignant neoplasm of palatopharyngeal arch

2 8166 B17..00 Malignant neoplasm of pancreas

2 34388 B17z.00 Malignant neoplasm of pancreas NOS

2 35535 B173.00 Malignant neoplasm of pancreatic duct

2 46153 B443.00 Malignant neoplasm of parametrium

2 4218 B541.00 Malignant neoplasm of parathyroid gland

2 72174 B4A4.00 Malignant neoplasm of paraurethral glands

2 54747 B300600 Malignant neoplasm of parietal bone

2 19226 B513.00 Malignant neoplasm of parietal lobe

2 64516 B18y400 Malignant neoplasm of parietal peritoneum

2 67107 B230.00 Malignant neoplasm of parietal pleura

2 4388 B020.00 Malignant neoplasm of parotid gland

2 54631 B306.00 Malignant neoplasm of pelvic bones, sacrum and coccyx

2 39413 B18y500 Malignant neoplasm of pelvic peritoneum

2 52316 B553.00 Malignant neoplasm of pelvis

2 55101 B553z00 Malignant neoplasm of pelvis NOS

2 38938 B306z00 Malignant neoplasm of pelvis, sacrum or coccyx NOS

2 63224 B48z.00 Malignant neoplasm of penis and other male genital organ NOS

2 3541 B48..00 Malignant neoplasm of penis and other male genital organs

2 43392 B483.00 Malignant neoplasm of penis, part unspecified

2	23480	B335900	Malignant neoplasm of perianal skin
2	94975	B241300	Malignant neoplasm of pericardium
2	65159	B180100	Malignant neoplasm of perinephric tissue
2	86046	B524400	Malignant neoplasm of peripheral nerve of abdomen
2	89258	B524200	Malignant neoplasm of peripheral nerve of low limb, incl hip
2	73988	B524500	Malignant neoplasm of peripheral nerve of pelvis
2	63695	B524300	Malignant neoplasm of peripheral nerve of thorax
2	61716	B524100	Malignant neoplasm of peripheral nerve,upp limb,incl should
2	63568	B524000	Malignant neoplasm of peripheral nerves of head, face & neck
2	58949	B308D00	Malignant neoplasm of phalanges of foot
2	86812	B305D00	Malignant neoplasm of phalanges of hand
2	37940	B072000	Malignant neoplasm of pharyngeal recess
2	46548	B071100	Malignant neoplasm of pharyngeal tonsil
2	16297	B0z0.00	Malignant neoplasm of pharynx unspecified
2	42460	B543.00	Malignant neoplasm of pineal gland
2	33271	B332200	Malignant neoplasm of pinna NEC
2	8550	B542000	Malignant neoplasm of pituitary gland
2	93762	B42..00	Malignant neoplasm of placenta
2	31573	B23..00	Malignant neoplasm of pleura
2	34742	B23z.00	Malignant neoplasm of pleura NOS
2	91240	B517300	Malignant neoplasm of pons
2	43548	B080.00	Malignant neoplasm of postcricoid region
2	92720	B243.00	Malignant neoplasm of posterior mediastinum
2	64462	B083.00	Malignant neoplasm of posterior pharynx
2	69671	B010.11	Malignant neoplasm of posterior third of tongue

2	95429	B071.00	Malignant neoplasm of posterior wall of nasopharynx
2	96869	B071z00	Malignant neoplasm of posterior wall of nasopharynx NOS
2	90124	B067.00	Malignant neoplasm of posterior wall of oropharynx
2	96802	B11y100	Malignant neoplasm of posterior wall of stomach NEC
2	42012	B494.00	Malignant neoplasm of posterior wall of urinary bladder
2	50681	B480.00	Malignant neoplasm of prepuce (foreskin)
2	48237	B111000	Malignant neoplasm of prepylorus of stomach
2	89916	B553100	Malignant neoplasm of presacral region
2	780	B46..00	Malignant neoplasm of prostate
2	51921	B306200	Malignant neoplasm of pubis
2	19318	B112.00	Malignant neoplasm of pyloric antrum of stomach
2	41215	B111100	Malignant neoplasm of pyloric canal of stomach
2	21620	B111.00	Malignant neoplasm of pylorus of stomach
2	59092	B111z00	Malignant neoplasm of pylorus of stomach NOS
2	39897	B081.00	Malignant neoplasm of pyriform sinus
2	92371	B304300	Malignant neoplasm of radius
2	27855	B140.00	Malignant neoplasm of rectosigmoid junction
2	1800	B141.00	Malignant neoplasm of rectum
2	35357	B14..00	Malignant neoplasm of rectum, rectosigmoid junction and anus
2	27540	B4A1000	Malignant neoplasm of renal calyces
2	12389	B4A1.00	Malignant neoplasm of renal pelvis
2	54184	B4A1z00	Malignant neoplasm of renal pelvis NOS
2	42569	B2zz.00	Malignant neoplasm of respiratory tract NOS
2	28069	B505.00	Malignant neoplasm of retina
2	24048	B180200	Malignant neoplasm of retrocaecal tissue

2	37724	B056.00	Malignant neoplasm of retromolar area
2	21330	B180.00	Malignant neoplasm of retroperitoneum
2	61555	B180z00	Malignant neoplasm of retroperitoneum NOS
2	44108	B18..00	Malignant neoplasm of retroperitoneum and peritoneum
2	16298	B18z.00	Malignant neoplasm of retroperitoneum and peritoneum NOS
2	37842	B303000	Malignant neoplasm of rib
2	51237	B303z00	Malignant neoplasm of rib, sternum and clavicle NOS
2	27528	B303.00	Malignant neoplasm of ribs, sternum and clavicle
2	69951	B055100	Malignant neoplasm of roof of mouth
2	94390	B070.00	Malignant neoplasm of roof of nasopharynx
2	40966	B306300	Malignant neoplasm of sacral vertebra
2	107126	B553200	Malignant neoplasm of sacrococcygeal region
2	37165	B334000	Malignant neoplasm of scalp
2	54234	B334.00	Malignant neoplasm of scalp and skin of neck
2	73760	B334z00	Malignant neoplasm of scalp or skin of neck NOS
2	49054	B304000	Malignant neoplasm of scapula
2	71810	B304.00	Malignant neoplasm of scapula and long bones of upper arm
2	47767	B486.00	Malignant neoplasm of scrotum
2	37016	B33..14	Malignant neoplasm of sebaceous gland
	111426	B308900	Malignant neoplasm of second metatarsal bone
2	68161	B48y000	Malignant neoplasm of seminal vesicle
2	62761	B200200	Malignant neoplasm of septum of nose
2	105475	B308.00	Malignant neoplasm of short bones of leg
2	103354	B308z00	Malignant neoplasm of short bones of leg NOS

2	2815	B133.00	Malignant neoplasm of sigmoid colon
2	2492	B33z.00	Malignant neoplasm of skin NOS
2	18618	B335300	Malignant neoplasm of skin of abdominal wall
2	64270	B337500	Malignant neoplasm of skin of ankle
2	33997	B332000	Malignant neoplasm of skin of auricle (ear)
2	70380	B335000	Malignant neoplasm of skin of axillary fold
2	45077	B335700	Malignant neoplasm of skin of back
2	30543	B335200	Malignant neoplasm of skin of breast
2	62305	B335800	Malignant neoplasm of skin of buttock
2	30645	B333000	Malignant neoplasm of skin of cheek, external
2	37969	B335100	Malignant neoplasm of skin of chest, excluding breast
2	49403	B333100	Malignant neoplasm of skin of chin
2	62080	B332100	Malignant neoplasm of skin of external auditory meatus
2	55670	B333200	Malignant neoplasm of skin of eyebrow
2	25245	B336400	Malignant neoplasm of skin of finger
2	70587	B337700	Malignant neoplasm of skin of foot
2	30577	B336200	Malignant neoplasm of skin of fore-arm
2	30576	B333300	Malignant neoplasm of skin of forehead
2	67914	B337900	Malignant neoplasm of skin of great toe
2	66319	B335500	Malignant neoplasm of skin of groin
2	54352	B336300	Malignant neoplasm of skin of hand
2	104025	B337600	Malignant neoplasm of skin of heel
2	70988	B337000	Malignant neoplasm of skin of hip
2	56954	B337200	Malignant neoplasm of skin of knee
2	18245	B330.00	Malignant neoplasm of skin of lip

2	33682	B337400	Malignant neoplasm of skin of lower leg
2	57442	B337.00	Malignant neoplasm of skin of lower limb and hip
2	61194	B337z00	Malignant neoplasm of skin of lower limb or hip NOS
2	43619	B334100	Malignant neoplasm of skin of neck
2	16202	B333400	Malignant neoplasm of skin of nose (external)
2	46458	B335600	Malignant neoplasm of skin of perineum
2	68197	B337300	Malignant neoplasm of skin of popliteal fossa area
2	66447	B335A00	Malignant neoplasm of skin of scapular region
2	43122	B336000	Malignant neoplasm of skin of shoulder
2	21327	B333500	Malignant neoplasm of skin of temple
2	58601	B337100	Malignant neoplasm of skin of thigh
2	64406	B336500	Malignant neoplasm of skin of thumb
2	65782	B337800	Malignant neoplasm of skin of toe
2	57446	B335.00	Malignant neoplasm of skin of trunk, excluding scrotum
2	15868	B335z00	Malignant neoplasm of skin of trunk, excluding scrotum, NOS
2	67748	B335400	Malignant neoplasm of skin of umbilicus
2	42707	B336100	Malignant neoplasm of skin of upper arm
2	30747	B336.00	Malignant neoplasm of skin of upper limb and shoulder
2	60526	B336z00	Malignant neoplasm of skin of upper limb or shoulder NOS
2	43390	B12z.00	Malignant neoplasm of small intestine NOS
2	6806	B12..00	Malignant neoplasm of small intestine and duodenum
2	40292	B053.00	Malignant neoplasm of soft palate
2	40014	B310100	Malignant neoplasm of soft tissue of face
2	59382	B310000	Malignant neoplasm of soft tissue of head
2	48517	B310200	Malignant neoplasm of soft tissue of neck

2	46613	B18y.00	Malignant neoplasm of specified parts of peritoneum
2	64106	B18yz00	Malignant neoplasm of specified parts of peritoneum NOS
2	60052	B55yz00	Malignant neoplasm of specified site NOS
2	95783	B17yz00	Malignant neoplasm of specified site of pancreas NOS
2	63331	B485.00	Malignant neoplasm of spermatic cord
2	55595	B300700	Malignant neoplasm of sphenoid bone
2	65215	B205.00	Malignant neoplasm of sphenoidal sinus
2	105613	B161300	Malignant neoplasm of sphincter of Oddi
2	51115	B522.00	Malignant neoplasm of spinal cord
2	49714	B523.00	Malignant neoplasm of spinal meninges
2	67211	B523z00	Malignant neoplasm of spinal meninges NOS
2	65460	B1z1.00	Malignant neoplasm of spleen NEC
2	93778	B1z1z00	Malignant neoplasm of spleen NOS
2	18619	B137.00	Malignant neoplasm of splenic flexure of colon
2	57719	B41y100	Malignant neoplasm of squamocolumnar junction of cervix
2	49491	B303100	Malignant neoplasm of sternum
2	8386	B11..00	Malignant neoplasm of stomach
2	14800	B11z.00	Malignant neoplasm of stomach NOS
2	22441	B212.00	Malignant neoplasm of subglottis
2	70928	B022.00	Malignant neoplasm of sublingual gland
2	51786	B021.00	Malignant neoplasm of submandibular gland
2	73510	B550500	Malignant neoplasm of supraclavicular fossa NOS
2	26165	B211.00	Malignant neoplasm of supraglottis
2	40443	B33..15	Malignant neoplasm of sweat gland
2	39870	B172.00	Malignant neoplasm of tail of pancreas

2	95182	B308100	Malignant neoplasm of talus
2	49463	B310400	Malignant neoplasm of tarsus of eyelid
2	62104	B300800	Malignant neoplasm of temporal bone
2	46792	B512.00	Malignant neoplasm of temporal lobe
2	47556	B512z00	Malignant neoplasm of temporal lobe NOS
2	15148	B47..00	Malignant neoplasm of testis
2	38510	B47z.00	Malignant neoplasm of testis NOS
2	62126	B510500	Malignant neoplasm of thalamus
2	69821	B18y600	Malignant neoplasm of the pouch of Douglas
2	108638	B305A00	Malignant neoplasm of third metacarpal bone
2	41362	B101.00	Malignant neoplasm of thoracic oesophagus
2	32372	B302100	Malignant neoplasm of thoracic vertebra
2	47286	B551.00	Malignant neoplasm of thorax
2	64810	B551z00	Malignant neoplasm of thorax NOS
2	27483	B240.00	Malignant neoplasm of thymus
2	62556	B24..00	Malignant neoplasm of thymus, heart and mediastinum
2	47862	B213300	Malignant neoplasm of thyroid cartilage
2	5637	B53..00	Malignant neoplasm of thyroid gland
2	40814	B307200	Malignant neoplasm of tibia
2	10283	B01..00	Malignant neoplasm of tongue
2	40557	B01z.00	Malignant neoplasm of tongue NOS
2	37096	B015.00	Malignant neoplasm of tongue, junctional zone
2	36161	B012.00	Malignant neoplasm of tongue, tip and lateral border
2	16241	B060.00	Malignant neoplasm of tonsil
2	24397	B061.00	Malignant neoplasm of tonsillar fossa

2	100002	B062z00	Malignant neoplasm of tonsillar fossa NOS
2	55066	B062.00	Malignant neoplasm of tonsillar pillar
2	15221	B220.00	Malignant neoplasm of trachea
2	37810	B220z00	Malignant neoplasm of trachea NOS
2	13243	B22..00	Malignant neoplasm of trachea, bronchus and lung
2	6935	B131.00	Malignant neoplasm of transverse colon
2	38862	B490.00	Malignant neoplasm of trigone of urinary bladder
2	67217	B55y100	Malignant neoplasm of trunk NOS
2	47668	B48y100	Malignant neoplasm of tunica vaginalis
2	54613	B201200	Malignant neoplasm of tympanic antrum
2	98537	B201100	Malignant neoplasm of tympanic cavity
2	64848	B304400	Malignant neoplasm of ulna
2	64602	B470.00	Malignant neoplasm of undescended testis
2	96429	B470z00	Malignant neoplasm of undescended testis NOS
6	47810	B59..00	Malignant neoplasm of unspecified site
6	54267	B59z.00	Malignant neoplasm of unspecified site NOS
2	95772	B051000	Malignant neoplasm of upper buccal sulcus
2	55550	B331100	Malignant neoplasm of upper eyelid
2	32024	B030.00	Malignant neoplasm of upper gum
2	27449	B554.00	Malignant neoplasm of upper limb NOS
	111289	B002000	Malignant neoplasm of upper lip, buccal aspect
2	66270	B000000	Malignant neoplasm of upper lip, external
2	99001	B002100	Malignant neoplasm of upper lip, frenulum
2	99493	B002.00	Malignant neoplasm of upper lip, inner aspect
2	100721	B002z00	Malignant neoplasm of upper lip, inner aspect NOS

2	50296	B000100	Malignant neoplasm of upper lip, lipstick area
2	98500	B002200	Malignant neoplasm of upper lip, mucosa
2	90610	B002300	Malignant neoplasm of upper lip, oral aspect
2	73962	B000.00	Malignant neoplasm of upper lip, vermilion border
2	98740	B000z00	Malignant neoplasm of upper lip, vermilion border NOS
2	31700	B222000	Malignant neoplasm of upper lobe bronchus
2	25886	B222100	Malignant neoplasm of upper lobe of lung
2	10358	B222.00	Malignant neoplasm of upper lobe, bronchus or lung
2	44169	B222z00	Malignant neoplasm of upper lobe, bronchus or lung NOS
2	50789	B103.00	Malignant neoplasm of upper third of oesophagus
2	29826	B342.00	Malignant neoplasm of upper-inner quadrant of female breast
2	23399	B344.00	Malignant neoplasm of upper-outer quadrant of female breast
2	42023	B497.00	Malignant neoplasm of urachus
2	15223	B4A2.00	Malignant neoplasm of ureter
2	28241	B496.00	Malignant neoplasm of ureteric orifice
2	101608	B4A1100	Malignant neoplasm of ureteropelvic junction
2	15644	B4A3.00	Malignant neoplasm of urethra
2	779	B49..00	Malignant neoplasm of urinary bladder
2	31102	B49z.00	Malignant neoplasm of urinary bladder NOS
2	65106	B44z.00	Malignant neoplasm of uterine adnexa NOS
2	2744	B40..00	Malignant neoplasm of uterus, part unspecified
2	37516	B054.00	Malignant neoplasm of uvula
2	37328	B450.00	Malignant neoplasm of vagina
2	60772	B450z00	Malignant neoplasm of vagina NOS
2	10698	B450100	Malignant neoplasm of vaginal vault

2	39554	B063.00	Malignant neoplasm of vallecula
2	62840	B013.00	Malignant neoplasm of ventral surface of tongue
2	38488	B013z00	Malignant neoplasm of ventral tongue surface NOS
2	16704	B302.00	Malignant neoplasm of vertebral column
2	49701	B302z00	Malignant neoplasm of vertebral column NOS
2	103796	B051.00	Malignant neoplasm of vestibule of mouth
2	62182	B200300	Malignant neoplasm of vestibule of nose
2	106194	B231.00	Malignant neoplasm of visceral pleura
2	44452	B300C00	Malignant neoplasm of vomer
2	4554	B454.00	Malignant neoplasm of vulva unspecified
2	54493	B303500	Malignant neoplasm of xiphoid process
2	50299	B300900	Malignant neoplasm of zygomatic bone
2	60312	B16y.00	Malignant neoplasm other gallbladder/extrahepatic bile duct
2	56918	B1zy.00	Malignant neoplasm other spec digestive tract and peritoneum
2	42429	B33X.00	Malignant neoplasm overlapping lesion of skin
2	59823	B542.00	Malignant neoplasm pituitary gland and craniopharyngeal duct
2	99386	B073200	Malignant neoplasm posterior margin nasal septum and choanae
2	50974	B14z.00	Malignant neoplasm rectum,rectosigmoid junction and anus NOS
2	53515	B332.00	Malignant neoplasm skin of ear and external auricular canal
2	27370	B333.00	Malignant neoplasm skin of other and unspecified parts face
2	46008	B333z00	Malignant neoplasm skin other and unspec part of face NOS
2	108389	B310500	Malignant neoplasm soft tissues of cervical spine
2	53884	B060z00	Malignant neoplasm tonsil NOS
	111311	B317.00	Malignant neoplasm, overlap lesion connective & soft tissue

2	66646	B26..00	Malignant neoplasm, overlap lesion of resp & intrathor orgs
2	68824	B48y200	Malignant neoplasm, overlapping lesion male genital orgs
2	39590	B206.00	Malignant neoplasm, overlapping lesion of accessory sinuses
2	35039	B163.00	Malignant neoplasm, overlapping lesion of biliary tract
2	47801	B49y000	Malignant neoplasm, overlapping lesion of bladder
2	65241	B51y200	Malignant neoplasm, overlapping lesion of brain
2	49148	B347.00	Malignant neoplasm, overlapping lesion of breast
2	58094	B412.00	Malignant neoplasm, overlapping lesion of cervix uteri
2	93478	B138.00	Malignant neoplasm, overlapping lesion of colon
2	94776	B1z2.00	Malignant neoplasm, overlapping lesion of digestive system
2	45922	B508.00	Malignant neoplasm, overlapping lesion of eye and adnexa
2	17912	B042.00	Malignant neoplasm, overlapping lesion of floor of mouth
2	50579	B214.00	Malignant neoplasm, overlapping lesion of larynx
2	66422	B074.00	Malignant neoplasm, overlapping lesion of nasopharynx
2	67497	B106.00	Malignant neoplasm, overlapping lesion of oesophagus
2	97875	B175.00	Malignant neoplasm, overlapping lesion of pancreas
2	52570	B487.00	Malignant neoplasm, overlapping lesion of penis
2	66166	B124.00	Malignant neoplasm, overlapping lesion of small intestine
2	51690	B117.00	Malignant neoplasm, overlapping lesion of stomach
2	50777	B524600	Malignant neoplasm,overlap lesion periph nerve & auton ns
2	87113	B54X.00	Malignant neoplasm-pluriglandular involvement,unspecified
2	43614	B30X.00	Malignant neoplasm/bones+articular cartilage/limb,unspfd
2	67451	B30W.00	Malignant neoplasm/overlap lesion/bone+articulr cartilage
2	26454	B45X.00	Malignant neoplasm/overlapping lesion/feml genital organs
6	51352	B592.00	Malignant neoplasms of independent (primary) multiple sites

2	65434	B62z.00	Malignant neoplasms of lymphoid and histiocytic tissue NOS
2	47205	B017.00	Malignant overlapping lesion of tongue
2	22158	B630000	Malignant plasma cell neoplasm, extramedullary plasmacytoma
2	62437	B62x400	Malignant reticulosis
2	50152	B306500	Malignant sacral teratoma
1	52236	C10A.00	Malnutrition-related diabetes mellitus
1	66675	C10A000	Malnutrition-related diabetes mellitus with coma
1	33969	C10A100	Malnutrition-related diabetes mellitus with ketoacidosis
1	67709	H354.00	Malt workers' lung
1	56652	H356.00	Maple bark strippers' lung
1	89206	H423.00	Massive silicotic fibrosis
2	65721	B673.00	Mast cell leukaemia
2	100615	B626500	Mast cell malignancy of lymph nodes inguinal region and leg
2	31324	B626800	Mast cell malignancy of lymph nodes of multiple sites
2	103900	B626000	Mast cell malignancy of unspecified site
1	14889	C100111	Maturity onset diabetes
1	59991	C10D.11	Maturity onset diabetes in youth type 2
2	57671	B672.00	Megakaryocytic leukaemia
2	12465	K032.00	Membranoproliferative nephritis unspecified
2	41881	K032y14	Mesangiocapillary glomerulonephritis NEC
2	36342	K032y13	Mesangioproliferative glomerulonephritis NEC
2	7484	B226.00	Mesothelioma
2	101885	B241400	Mesothelioma of pericardium
2	17874	B181.00	Mesothelioma of peritoneum

2	9600	B232.00	Mesothelioma of pleura
6	6471	B57..11	Metastases of respiratory and/or digestive systems
1	3018	663V100	Mild asthma
1	25796	H332.00	Mixed asthma
1	24248	H313.00	Mixed simple and mucopurulent chronic bronchitis
1	13065	663V200	Moderate asthma
2	67700	B66..12	Monoblastic leukaemia
2	35875	B66..00	Monocytic leukaemia
2	93342	B66z.00	Monocytic leukaemia NOS
1	11150	H311.00	Mucopurulent chronic bronchitis
1	61513	H311z00	Mucopurulent chronic bronchitis NOS
1	8634	E004.11	Multi infarct dementia
1	69204	J615100	Multilobular portal cirrhosis
1	98642	G633.00	Multiple and bilateral precerebral arterial occlusion
1	52323	J11z.12	Multiple gastric ulcers
2	4944	B630.00	Multiple myeloma
2	37182	B63..00	Multiple myeloma and immunoproliferative neoplasms
1	17085	N240200	Muscular rheumatism
1	41694	H355.00	Mushroom workers' lung
2	39420	F381300	Myasthenic syndrome due to diabetic amyotrophy
2	12006	B621.00	Mycosis fungoides
2	38005	B621z00	Mycosis fungoides NOS
2	91674	B621300	Mycosis fungoides of intra-abdominal lymph nodes
2	96379	B621400	Mycosis fungoides of lymph nodes of axilla and upper limb
2	72714	B621500	Mycosis fungoides of lymph nodes of inguinal region and leg

2	95012	B621800	Mycosis fungoides of lymph nodes of multiple sites
2	95949	B621000	Mycosis fungoides of unspecified site
2	7176	B65..00	Myeloid leukaemia
2	33344	B65z.00	Myeloid leukaemia NOS
2	70724	B653.00	Myeloid sarcoma
2	15211	B630.12	Myelomatosis
2	20440	B69..00	Myelomonocytic leukaemia
2	17056	B6y0.11	Myeloproliferative disease
2	6115	B6y0.00	Myeloproliferative disorder
2	39336	B6y1.00	Myelosclerosis with myeloid metaplasia
1	108072	F396100	Myopathy due to disseminated lupus erythematosus
1	31209	F396400	Myopathy due to rheumatoid arthritis
1	55601	F396600	Myopathy due to scleroderma
1	5884	C109.11	NIDDM - Non-insulin dependent diabetes mellitus
1	56803	C107400	NIDDM with peripheral circulatory disorder
2	782	B....00	Neoplasms
2	35904	Bz...00	Neoplasms NOS
2	45700	By...00	Neoplasms otherwise specified
2	10647	K02..11	Nephritis - chronic
2	4850	K03..11	Nephritis and nephropathy unspecified
2	33580	K03..00	Nephritis and nephropathy unspecified
2	67193	K032y00	Nephritis unsp+OS membranoprolif glomerulonephritis lesion
2	94350	K032z00	Nephritis unsp+membranoprolif glomerulonephritis lesion NOS
2	2773	K0...00	Nephritis, nephrosis and nephrotic syndrome

2	30310	K081.00	Nephrogenic diabetes insipidus
2	11875	K02..12	Nephropathy - chronic
2	21989	K019.00	Nephrotic syn,diffuse mesangiocapillary glomerulonephritis
1	47672	K01x400	Nephrotic syndrome in systemic lupus erythematosus
2	99644	K012.00	Nephrotic syndrome+membranoproliferative glomerulonephritis
2	5179	B620.00	Nodular lymphoma (Brill - Symmers disease)
2	65701	B620z00	Nodular lymphoma NOS
2	92068	B620300	Nodular lymphoma of intra-abdominal lymph nodes
2	105203	B620200	Nodular lymphoma of intrathoracic lymph nodes
2	45264	B620100	Nodular lymphoma of lymph nodes of head, face and neck
2	94995	B620500	Nodular lymphoma of lymph nodes of inguinal region and leg
2	58082	B620800	Nodular lymphoma of lymph nodes of multiple sites
2	66327	B620000	Nodular lymphoma of unspecified site
2	3604	B627.00	Non - Hodgkin's lymphoma
2	10755	F420600	Non proliferative diabetic retinopathy
1	16455	J615z00	Non-alcoholic cirrhosis NOS
2	69278	C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
2	40962	C109H00	Non-insulin dependent d m with neuropathic arthropathy
1	506	C100112	Non-insulin dependent diabetes mellitus
1	4513	C109.00	Non-insulin dependent diabetes mellitus
1	8403	C109700	Non-insulin dependent diabetes mellitus - poor control
1	24693	C109G00	Non-insulin dependent diabetes mellitus with arthropathy
1	40401	C109500	Non-insulin dependent diabetes mellitus with gangrene
1	43785	C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma

2	72320	C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
2	59365	C109C00	Non-insulin dependent diabetes mellitus with nephropathy
2	45467	C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
1	34912	C109400	Non-insulin dependent diabetes mellitus with ulcer
1	62146	C109300	Non-insulin-dependent diabetes mellitus with multiple comps
2	55842	C109200	Non-insulin-dependent diabetes mellitus with neuro comps
2	50429	C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
2	52303	C109000	Non-insulin-dependent diabetes mellitus with renal comps
2	17262	C109600	Non-insulin-dependent diabetes mellitus with retinopathy
1	29979	C109900	Non-insulin-dependent diabetes mellitus without complication
1	15205	N2z..00	Nonarticular rheumatism NOS
1	45284	2A42.00	O/E - ankle reflex abnormal
2	9835	2BBL.00	O/E - diabetic maculopathy present both eyes
1	11680	2I16.00	O/E - gangrene
2	22135	2833.00	O/E - hemiplegia
2	11129	2BBQ.00	O/E - left eye background diabetic retinopathy
2	13103	2BBS.00	O/E - left eye preproliferative diabetic retinopathy
2	13101	2BBV.00	O/E - left eye proliferative diabetic retinopathy
2	52041	2BBl.00	O/E - left eye stable treated prolif diabetic retinopathy
2	36133	2835.00	O/E - paraplegia
2	11433	2BBP.00	O/E - right eye background diabetic retinopathy
2	13099	2BBR.00	O/E - right eye preproliferative diabetic retinopathy
2	47328	2BBk.00	O/E - right eye stable treated prolif diabetic retinopathy

1	63216	H464100	Obliterative bronchiolitis due to chemical fumes
1	27819	H312.00	Obstructive chronic bronchitis
1	44525	H312z00	Obstructive chronic bronchitis NOS
1	3458	663V000	Occasional asthma
1	71274	G677400	Occlusion+stenosis of multiple and bilat cerebral arteries
1	22752	173c.00	Occupational asthma
2	4865	B10z.11	Oesophageal cancer
3	1641	G85..11	Oesophageal varices
3	10797	G858.00	Oesophageal varices NOS
3	8363	G852300	Oesophageal varices in alcoholic cirrhosis of the liver
3	26319	G852200	Oesophageal varices in cirrhosis of the liver
3	44424	G852.00	Oesophageal varices in diseases EC
3	62582	G852z00	Oesophageal varices in diseases EC NOS
3	24989	G850.00	Oesophageal varices with bleeding
3	96756	G852000	Oesophageal varices with bleeding in diseases EC
3	30655	G851.00	Oesophageal varices without bleeding
3	73139	G852100	Oesophageal varices without bleeding in diseases EC
1	4017	G32..00	Old myocardial infarction
1	96717	S621.00	Open traumatic subarachnoid haemorrhage
1	33914	761Jz00	Operation on gastric ulcer NOS
1	5928	7627.00	Operations on duodenal ulcer
1	23688	761J.00	Operations on gastric ulcer
2	29735	B30..12	Osteoma
2	19437	B30z000	Osteosarcoma
2	44318	B62xX00	Oth and unspecif peripheral & cutaneous T-cell lymphomas

1	34803	G30y.00	Other acute myocardial infarction
1	46017	G30yz00	Other acute myocardial infarction NOS
2	35235	K04y.00	Other acute renal failure
1	51858	H35y.00	Other allergic alveolitis
1	55552	H35yz00	Other allergic alveolitis NOS
2	94174	B67y.00	Other and unspecified leukaemia
2	99413	B67yz00	Other and unspecified leukaemia NOS
1	13577	G67..00	Other cerebrovascular disease
1	37493	G67z.00	Other cerebrovascular disease NOS
1	34117	G67y.00	Other cerebrovascular disease OS
1	66043	H31y.00	Other chronic bronchitis
1	68066	H31yz00	Other chronic bronchitis NOS
2	63615	K02yz00	Other chronic glomerulonephritis NOS
1	40788	H32y.00	Other emphysema
1	16410	H32yz00	Other emphysema NOS
2	64567	B63y.00	Other immunoproliferative neoplasms
2	50804	K08yz00	Other impaired renal function disorder NOS
2	34692	B68y.00	Other leukaemia of unspecified cell type
2	49725	B64y.00	Other lymphoid leukaemia
2	38331	B64yz00	Other lymphoid leukaemia NOS
6	26034	B591.00	Other malignant neoplasm NOS
2	33333	B62..00	Other malignant neoplasm of lymphoid and histiocytic tissue
2	4632	B33..00	Other malignant neoplasm of skin
2	99015	B66y.00	Other monocytic leukaemia
2	103645	B66yz00	Other monocytic leukaemia NOS

2	66089	B65yz00	Other myeloid leukaemia NOS
1	5943	G73..00	Other peripheral vascular disease
1	51326	G63y.00	Other precerebral artery occlusion
3	48102	J62y.00	Other sequelae of chronic liver disease
1	5387	G301.00	Other specified anterior myocardial infarction
1	51311	G6y..00	Other specified cerebrovascular disease
1	59288	C103y00	Other specified diabetes mellitus with coma
1	38617	C101y00	Other specified diabetes mellitus with ketoacidosis
2	61523	C106y00	Other specified diabetes mellitus with neurological comps
2	47377	C105y00	Other specified diabetes mellitus with ophthalmic complicatn
1	10098	C10yy00	Other specified diabetes mellitus with other spec comps
2	13279	C104y00	Other specified diabetes mellitus with renal complications
1	64283	C10zy00	Other specified diabetes mellitus with unspecified comps
2	37272	B67..00	Other specified leukaemia
2	30632	B67z.00	Other specified leukaemia NOS
1	35759	N2y..00	Other specified nonarticular rheumatism
1	94104	761Jy00	Other specified operation on gastric ulcer
1	38907	G73y.00	Other specified peripheral vascular disease
1	4325	G73yz00	Other specified peripheral vascular disease NOS
2	99887	B60y.00	Other specified reticulosarcoma or lymphosarcoma
3	89587	A704z00	Other specified viral hepatitis with hepatic coma NOS
1	19354	G65y.00	Other transient cerebral ischaemia
2	10314	B057.00	Overlapping lesion of other and unspecified parts of mouth
2	101907	B182.00	Overlapping malign lesion of retroperitoneum and peritoneum

2	96585	B32y000	Overlapping malignant melanoma of skin
2	20170	B222.11	Pancoast's syndrome
1	46578	H321.00	Panlobular emphysema
2	3063	F241.00	Paraplegia
2	99040	F230.11	Paraplegia - congenital
6	18676	B585000	Pathological fracture due to metastatic bone disease
1	12213	8BL2.00	Patient on maximal tolerated therapy for diabetes
1	670	J13..00	Peptic ulcer - (PU) site unspecified
1	19928	J13z.00	Peptic ulcer NOS
1	24021	J102000	Peptic ulcer of oesophagus
1	4643	1956.00	Peptic ulcer symptoms
1	11104	J111211	Perforated chronic gastric ulcer
2	12464	B62x200	Peripheral T-cell lymphoma
1	9204	G732.00	Peripheral gangrene
1	5702	G73..11	Peripheral ischaemic vascular disease
1	3530	G73z.00	Peripheral vascular disease NOS
1	2760	G73zz00	Peripheral vascular disease NOS
1	17464	G32..12	Personal history of myocardial infarction
2	18231	B540.11	Phaeochromocytoma
2	68114	K080000	Phosphate-losing tubular disorders
1	31447	H352100	Pigeon-fanciers' lung
1	8206	C350012	Pigmentary cirrhosis of liver
1	45427	H35y500	Pituitary snuff-takers' disease
2	39187	B631.00	Plasma cell leukaemia
2	21329	B630200	Plasmacytoma NOS

1	5005	H410.00	Pleural plaque disease due to asbestosis
1	31423	H45..00	Pneumoconiosis NOS
1	23461	H43z.00	Pneumoconiosis due to inorganic dust NOS
1	65376	H43..00	Pneumoconiosis due to other inorganic dust
1	7731	H330.14	Pollen asthma
1	1408	N20..00	Polymyalgia rheumatica
1	15511	N004.00	Polymyositis
1	93927	N231400	Polymyositis ossificans
2	63555	F374z00	Polyneuropathy in disease NOS
1	62401	F371200	Polyneuropathy in rheumatoid arthritis
1	47257	J615.11	Portal cirrhosis
1	55454	J615y00	Portal cirrhosis unspecified
1	40963	J61y300	Portal fibrosis without cirrhosis
3	5129	J623.00	Portal hypertension
1	41491	H341.00	Post-infective bronchiectasis
1	50960	L180500	Pre-existing diabetes mellitus, insulin-dependent
1	50609	L180600	Pre-existing diabetes mellitus, non-insulin-dependent
1	55431	L180X00	Pre-existing diabetes mellitus, unspecified
1	45781	G63..00	Precerebral arterial occlusion
1	71585	G63z.00	Precerebral artery occlusion NOS
2	2986	F420200	Preproliferative diabetic retinopathy
1	6333	J11..11	Prepyloric ulcer
1	15165	E001.00	Presenile dementia
1	38438	E001z00	Presenile dementia NOS
1	40068	G731100	Presenile gangrene

2	68410	B150200	Primary angiosarcoma of liver
1	5638	J616000	Primary biliary cirrhosis
2	16126	B150000	Primary carcinoma of liver
2	25535	B150.00	Primary malignant neoplasm of liver
2	44399	B150z00	Primary malignant neoplasm of liver NOS
6	11035	B593.00	Primary malignant neoplasm of unknown site
2	11991	B454.11	Primary vulval cancer
1	44141	N001000	Progressive systemic sclerosis
2	3286	F420100	Proliferative diabetic retinopathy
2	31586	B64y100	Prolymphocytic leukaemia
1	40159	H311000	Purulent chronic bronchitis
1	3101	J11..12	Pyloric ulcer
2	5901	B141.12	Rectal carcinoma
1	20364	H340.00	Recurrent bronchiectasis
1	29317	J124.00	Recurrent duodenal ulcer
1	53480	J614300	Recurrent hepatitis
2	41676	K034.00	Renal cortical necrosis unspecified
2	34648	K080100	Renal dwarfism
2	350	K06..00	Renal failure unspecified
2	50728	K080200	Renal infantilism
2	18712	B4A..11	Renal malignant neoplasm
2	45867	K035.00	Renal medullary necrosis unspecified
2	29638	K080.00	Renal osteodystrophy
2	34637	K080z00	Renal osteodystrophy NOS
2	66062	K080300	Renal rickets

1	64710	7612500	Resection of gastric ulcer by cautery
2	1481	B600.00	Reticulosarcoma
2	99240	B600z00	Reticulosarcoma NOS
2	70374	B600300	Reticulosarcoma of intra-abdominal lymph nodes
2	71031	B600100	Reticulosarcoma of lymph nodes of head, face and neck
2	95058	B600700	Reticulosarcoma of spleen
2	60242	B600000	Reticulosarcoma of unspecified site
2	99951	B60z.00	Reticulosarcoma or lymphosarcoma NOS
1	33474	N240.00	Rheumatism and fibrositis unspecified
1	35937	N240z00	Rheumatism or fibrositis NOS
1	1029	N240000	Rheumatism unspecified
1	844	N040.00	Rheumatoid arthritis
1	27603	N04..00	Rheumatoid arthritis and other inflammatory polyarthropathy
1	51238	N040K00	Rheumatoid arthritis of 1st MTP joint
1	63198	N040A00	Rheumatoid arthritis of DIP joint of finger
1	107112	N040M00	Rheumatoid arthritis of IP joint of toe
1	42299	N040800	Rheumatoid arthritis of MCP joint
1	41941	N040900	Rheumatoid arthritis of PIP joint of finger
1	100914	N040400	Rheumatoid arthritis of acromioclavicular joint
1	51239	N040F00	Rheumatoid arthritis of ankle
1	63365	N040600	Rheumatoid arthritis of distal radio-ulnar joint
1	59738	N040500	Rheumatoid arthritis of elbow
1	49067	N040B00	Rheumatoid arthritis of hip
1	50863	N040D00	Rheumatoid arthritis of knee
1	99414	N040L00	Rheumatoid arthritis of lesser MTP joint

1	71784	N040J00	Rheumatoid arthritis of other tarsal joint
1	100776	N040C00	Rheumatoid arthritis of sacro-iliac joint
1	21358	N040200	Rheumatoid arthritis of shoulder
1	107963	N040300	Rheumatoid arthritis of sternoclavicular joint
1	73619	N040G00	Rheumatoid arthritis of subtalar joint
1	70658	N040H00	Rheumatoid arthritis of talonavicular joint
1	107791	N040E00	Rheumatoid arthritis of tibio-fibular joint
1	48832	N040700	Rheumatoid arthritis of wrist
1	43816	G5yA.00	Rheumatoid carditis
1	9954	H570.00	Rheumatoid lung
1	31724	N04y000	Rheumatoid lung
1	46436	N042100	Rheumatoid lung disease
1	10079	G580.12	Right heart failure
2	3293	F223.00	Right hemiplegia
1	19201	G61X100	Right sided intracerebral haemorrhage, unspecified
3	47214	760F300	Rigid oesophagoscopic injection sclerotherapy oesoph varices
1	13572	G713.11	Ruptured abdominal aortic aneurysm
1	15304	G715.00	Ruptured aortic aneurysm NOS
1	29939	G600.00	Ruptured berry aneurysm
1	63920	G713000	Ruptured suprarenal aortic aneurysm
1	16800	G711.11	Ruptured thoracic aortic aneurysm
2	12539	B3...12	Sarcoma of bone and connective tissue
1	3670	N001.00	Scleroderma
6	25366	B561300	Secondary and unspec malig neop ant mediastinal lymph nodes

6	44627	B560800	Secondary and unspec malig neop anterior cervical LN
6	50199	B563.00	Secondary and unspec malig neop axilla and upper limb LN
6	73538	B563z00	Secondary and unspec malig neop axilla and upper limb LN NOS
6	37540	B563000	Secondary and unspec malig neop axillary lymph nodes
6	62124	B561800	Secondary and unspec malig neop bronchopulmonary lymph nodes
6	101662	B565200	Secondary and unspec malig neop circumflex iliac LN
6	41691	B562000	Secondary and unspec malig neop coeliac lymph nodes
6	18658	B562300	Secondary and unspec malig neop common iliac lymph nodes
6	68611	B560900	Secondary and unspec malig neop deep cervical LN
6	61289	B564100	Secondary and unspec malig neop deep inguinal lymph nodes
6	92703	B560400	Secondary and unspec malig neop deep parotid lymph nodes
6	95378	B561200	Secondary and unspec malig neop diaphragmatic lymph nodes
6	69132	B562400	Secondary and unspec malig neop external iliac lymph nodes
6	61677	B562200	Secondary and unspec malig neop inferior mesenteric LN
6	69392	B561700	Secondary and unspec malig neop inferior tracheobronchial LN
6	50904	B563200	Secondary and unspec malig neop infraclavicular lymph nodes
6	63915	B564.00	Secondary and unspec malig neop inguinal and lower limb LN
6	105953	B561100	Secondary and unspec malig neop intercostal lymph nodes
6	84368	B565000	Secondary and unspec malig neop internal iliac lymph nodes
6	37919	B561000	Secondary and unspec malig neop internal mammary lymph nodes
6	44931	B562z00	Secondary and unspec malig neop intra-abdominal LN NOS
6	52736	B562.00	Secondary and unspec malig neop intra-abdominal lymph nodes

6	72803	B565z00	Secondary and unspec malig neop intrapelvic LN NOS
6	6701	B565.00	Secondary and unspec malig neop intrapelvic lymph nodes
6	93716	B561z00	Secondary and unspec malig neop intrathoracic LN NOS
6	64116	B561.00	Secondary and unspec malig neop intrathoracic lymph nodes
6	15507	B56z.00	Secondary and unspec malig neop lymph nodes NOS
6	49214	B560.00	Secondary and unspec malig neop lymph nodes head/face/neck
6	20159	B56y.00	Secondary and unspec malig neop lymph nodes multiple sites
6	28059	B560600	Secondary and unspec malig neop of facial lymph nodes
6	70747	B564z00	Secondary and unspec malig neop of inguinal and leg LN NOS
6	64918	B560000	Secondary and unspec malig neop of superficial parotid LN
6	58692	B561500	Secondary and unspec malig neop paratracheal lymph nodes
6	46409	B563300	Secondary and unspec malig neop pectoral lymph nodes
6	55463	B561400	Secondary and unspec malig neop post mediastinal lymph nodes
6	52190	B561900	Secondary and unspec malig neop pulmonary lymph nodes
6	47366	B565300	Secondary and unspec malig neop sacral lymph nodes
6	39433	B560500	Secondary and unspec malig neop submandibular lymph nodes
6	38343	B560700	Secondary and unspec malig neop submental lymph nodes
6	67797	B561600	Secondary and unspec malig neop superfic tracheobronchial LN
6	33395	B560200	Secondary and unspec malig neop superficial cervical LN
6	54278	B564000	Secondary and unspec malig neop superficial inguinal LN
6	72713	B562100	Secondary and unspec malig neop superficial mesenteric LN
6	98626	B563100	Secondary and unspec malig neop supratrochlear lymph nodes

6 66775 B560100 Secondary and unspec malignant neoplasm mastoid lymph nodes

6 65253 B560300 Secondary and unspec malignant neoplasm occipital lymph node

6 9618 B56..00 Secondary and unspecified malignant neoplasm of lymph nodes

1 15424 J616100 Secondary biliary cirrhosis

6 97832 B58y211 Secondary cancer of the cervix

6 65490 B58y411 Secondary cancer of the vulva

6 27651 B58..11 Secondary carcinoma of other specified sites

6 24301 B57..12 Secondary carcinoma of respiratory and/or digestive systems

1 22487 C10N.00 Secondary diabetes mellitus

6 36200 B575z00 Secondary malig neop of large intestine or rectum NOS

6 35053 B57..00 Secondary malig neop of respiratory and digestive systems

6 66083 B57z.00 Secondary malig neop of respiratory or digestive system NOS

6 67396 B576.00 Secondary malig neop of retroperitoneum and peritoneum

6 97672 B576z00 Secondary malig neop of retroperitoneum or peritoneum NOS

6 70026 B574z00 Secondary malig neop of small intestine or duodenum NOS

6 36401 B587.00 Secondary malignant neoplasm of adrenal gland

6 22146 B581100 Secondary malignant neoplasm of bladder

6 7654 B585.00 Secondary malignant neoplasm of bone and bone marrow

6 5198 B583000 Secondary malignant neoplasm of brain

6 33843 B583.00 Secondary malignant neoplasm of brain and spinal cord

6 59375 B583z00 Secondary malignant neoplasm of brain or spinal cord NOS

6 16760 B58y000 Secondary malignant neoplasm of breast

6 73616 B58y200 Secondary malignant neoplasm of cervix uteri

6 28727 B575000 Secondary malignant neoplasm of colon

6 55946 B574000 Secondary malignant neoplasm of duodenum

6 104480 B58y800 Secondary malignant neoplasm of epididymis and vas deferens

6 99511 B574200 Secondary malignant neoplasm of ileum

6 110433 B574100 Secondary malignant neoplasm of jejunum

6 1952 B580.00 Secondary malignant neoplasm of kidney

6 44529 B575.00 Secondary malignant neoplasm of large intestine and rectum

6 15103 B577.00 Secondary malignant neoplasm of liver

6 36147 B153.00 Secondary malignant neoplasm of liver

6 4137 B570.00 Secondary malignant neoplasm of lung

6 51551 B571.00 Secondary malignant neoplasm of mediastinum

6 56345 B57y.00 Secondary malignant neoplasm of other digestive organ

6 54120 B584.00 Secondary malignant neoplasm of other part of nervous system

6 62584 B573.00 Secondary malignant neoplasm of other respiratory organs

6 22524 B58yz00 Secondary malignant neoplasm of other specified site NOS

6 16500 B58z.00 Secondary malignant neoplasm of other specified site NOS

6 18616 B58y.00 Secondary malignant neoplasm of other specified sites

6 5842 B58..00 Secondary malignant neoplasm of other specified sites

6 62828 B581z00 Secondary malignant neoplasm of other urinary organ NOS

6 73213 B581.00 Secondary malignant neoplasm of other urinary organs

6 44615 B586.00 Secondary malignant neoplasm of ovary

6 49145 B58y700 Secondary malignant neoplasm of penis

6 27391 B576100 Secondary malignant neoplasm of peritoneum

6 16213 B572.00 Secondary malignant neoplasm of pleura

6	21590	B58y500	Secondary malignant neoplasm of prostate
6	62909	B575100	Secondary malignant neoplasm of rectum
6	35364	B576000	Secondary malignant neoplasm of retroperitoneum
6	19945	B582.00	Secondary malignant neoplasm of skin
6	55096	B582z00	Secondary malignant neoplasm of skin NOS
6	9505	B582600	Secondary malignant neoplasm of skin of breast
6	100296	B582100	Secondary malignant neoplasm of skin of face
6	43930	B582000	Secondary malignant neoplasm of skin of head
6	48828	B582500	Secondary malignant neoplasm of skin of hip and leg
6	35999	B582200	Secondary malignant neoplasm of skin of neck
6	63896	B582400	Secondary malignant neoplasm of skin of shoulder and arm
6	41144	B582300	Secondary malignant neoplasm of skin of trunk
6	64680	B574.00	Secondary malignant neoplasm of small intestine and duodenum
6	38918	B583100	Secondary malignant neoplasm of spinal cord
6	34145	B58y600	Secondary malignant neoplasm of testis
6	45824	B58y900	Secondary malignant neoplasm of tongue
6	54679	B594.00	Secondary malignant neoplasm of unknown site
6	60134	B581000	Secondary malignant neoplasm of ureter
6	53528	B581200	Secondary malignant neoplasm of urethra
6	55090	B58y100	Secondary malignant neoplasm of uterus
6	70736	B58y300	Secondary malignant neoplasm of vagina
6	60335	B58y400	Secondary malignant neoplasm of vulva
1	51697	C10G.00	Secondary pancreatic diabetes mellitus
6	67129	B560z00	Secondary unspec malig neop lymph nodes head/face/neck NOS

1	56860	H320000	Segmental bullous emphysema
2	21786	B471000	Seminoma of descended testis
2	2961	B47z.11	Seminoma of testis
2	7740	B470200	Seminoma of undescended testis
1	1916	E00..11	Senile dementia
1	1350	E00..12	Senile/presenile dementia
1	48149	G681.00	Sequelae of intracerebral haemorrhage
1	44740	G680.00	Sequelae of subarachnoid haemorrhage
1	51138	G68W.00	Sequelae/other + unspecified cerebrovascular diseases
1	93353	H35y600	Sequoiosis (red-cedar asthma)
1	10919	N04y111	Sero negative polyarthritis
1	6916	N040P00	Seronegative rheumatoid arthritis
1	9707	N047.00	Seropositive errosive rheumatoid arthritis
1	12019	N04X.00	Seropositive rheumatoid arthritis, unspecified
1	3366	663V300	Severe asthma
1	233	H33z011	Severe asthma attack
2	35014	B622.00	Sezary's disease
2	100532	B622z00	Sezary's disease NOS
1	30235	H434.00	Siderosis
1	17689	G30..17	Silent myocardial infarction
1	46460	H42..00	Silica and silicate pneumoconiosis
1	23446	H42z.00	Silica pneumoconiosis NOS
1	25603	H310.00	Simple chronic bronchitis
1	61118	H310z00	Simple chronic bronchitis NOS
1	16717	H310100	Smokers' cough

2	19028	B630100	Solitary myeloma
2	20122	F221.00	Spastic hemiplegia
2	9375	F241100	Spastic paraplegia
1	93577	H435.00	Stannosis
1	4892	H33z000	Status asthmaticus NOS
1	63830	G63..12	Stenosis of precerebral arteries
1	26108	C10B000	Steroid induced diabetes mellitus without complication
1	6865	761J.11	Stomach ulcer operations
1	1295	J14..15	Stomal ulcer
1	15821	J13..11	Stress ulcer NOS
1	18604	G61..12	Stroke due to intracerebral haemorrhage
2	54793	B682.00	Subacute leukaemia NOS
2	72774	B642.00	Subacute lymphoid leukaemia
2	101606	B662.00	Subacute monocytic leukaemia
2	63475	B652.00	Subacute myeloid leukaemia
2	104475	B692.00	Subacute myelomonocytic leukaemia
1	69313	J601200	Subacute yellow atrophy
1	17326	G60X.00	Subarachnoid haemorrh from intracranial artery, unspecif
1	1786	G60..00	Subarachnoid haemorrhage
1	23580	G60z.00	Subarachnoid haemorrhage NOS
1	28807	S62..12	Subarachnoid haemorrhage following injury
1	42331	G603.00	Subarachnoid haemorrhage from anterior communicating artery
1	41910	G605.00	Subarachnoid haemorrhage from basilar artery
1	56007	G601.00	Subarachnoid haemorrhage from carotid siphon and bifurcation

1	19412	G602.00	Subarachnoid haemorrhage from middle cerebral artery
1	9696	G604.00	Subarachnoid haemorrhage from posterior communicating artery
1	60692	G606.00	Subarachnoid haemorrhage from vertebral artery
1	20113	SK07.00	Subcutaneous emphysema
1	18912	G623.00	Subdural haemorrhage NOS
1	93206	H353.00	Suberosis (cork-handlers' lung)
1	70005	761J111	Suture of ulcer of stomach NEC
1	7871	N000.00	Systemic lupus erythematosus
1	42719	N000z00	Systemic lupus erythematosus NOS
1	29519	N000300	Systemic lupus erythematosus with organ or sys involv
1	11920	N000400	Systemic lupus erythematosus with pericarditis
1	28417	N001.12	Systemic sclerosis
1	110174	N001200	Systemic sclerosis induced by drugs and chemicals
2	90201	B62x000	T-zone lymphoma
1	60805	H420.00	Talc pneumoconiosis
2	9476	B471100	Teratoma of descended testis
2	15989	B47z.12	Teratoma of testis
2	36325	B470300	Teratoma of undescended testis
1	27563	G711.00	Thoracic aortic aneurysm which has ruptured
1	23532	G712.00	Thoracic aortic aneurysm without mention of rupture
1	11430	G715000	Thoracoabdominal aortic aneurysm, ruptured
1	40787	G716000	Thoracoabdominal aortic aneurysm, without mention of rupture
2	65777	B672.11	Thrombocytic leukaemia
1	44120	J635600	Toxic liver disease with fibrosis and cirrhosis of liver

1	3163	H300.00	Tracheobronchitis NOS
1	504	G65..00	Transient cerebral ischaemia
1	15788	G65zz00	Transient cerebral ischaemia NOS
1	1895	G65z.00	Transient cerebral ischaemia NOS
1	58545	S627.00	Traumatic subarachnoid haemorrhage
1	8181	S628.00	Traumatic subdural haemorrhage
2	95630	B62x600	True histiocytic lymphoma
1	63408	7A13411	Tube graft abdominal Aortic aneurysm (emergency)
1	26232	7A14411	Tube graft of Abdominal aortic aneurysm
1	17858	C108.12	Type 1 diabetes mellitus
1	1549	C10E.00	Type 1 diabetes mellitus
1	35288	C10E800	Type 1 diabetes mellitus - poor control
1	45914	C108812	Type 1 diabetes mellitus - poor control
1	40682	C10E900	Type 1 diabetes mellitus maturity onset
2	49554	C10EF00	Type 1 diabetes mellitus with diabetic cataract
1	69993	C10E600	Type 1 diabetes mellitus with gangrene
2	55239	C10EQ00	Type 1 diabetes mellitus with gastroparesis
1	39070	C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma
1	70766	C108E12	Type 1 diabetes mellitus with hypoglycaemic coma
1	10692	C10EM00	Type 1 diabetes mellitus with ketoacidosis
1	40837	C10EN00	Type 1 diabetes mellitus with ketoacidotic coma
2	68105	C10EB00	Type 1 diabetes mellitus with mononeuropathy
2	10418	C10ED00	Type 1 diabetes mellitus with nephropathy
2	61829	C108212	Type 1 diabetes mellitus with neurological complications
2	42831	C10E200	Type 1 diabetes mellitus with neurological complications

2	18230	C108J12	Type 1 diabetes mellitus with neuropathic arthropathy
2	47649	C10E100	Type 1 diabetes mellitus with ophthalmic complications
1	93468	C10EG00	Type 1 diabetes mellitus with peripheral angiopathy
1	30294	C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
1	30323	C10EK00	Type 1 diabetes mellitus with persistent proteinuria
2	46301	C10EC00	Type 1 diabetes mellitus with polyneuropathy
2	47582	C10E000	Type 1 diabetes mellitus with renal complications
2	21983	C108012	Type 1 diabetes mellitus with renal complications
2	41049	C108712	Type 1 diabetes mellitus with retinopathy
1	18683	C10E500	Type 1 diabetes mellitus with ulcer
1	69676	C10EA00	Type 1 diabetes mellitus without complication
1	758	C10F.00	Type 2 diabetes mellitus
1	17859	C109.12	Type 2 diabetes mellitus
1	25627	C10F700	Type 2 diabetes mellitus - poor control
1	45913	C109712	Type 2 diabetes mellitus - poor control
1	59253	C10FG00	Type 2 diabetes mellitus with arthropathy
1	49869	C109G12	Type 2 diabetes mellitus with arthropathy
2	44779	C109E12	Type 2 diabetes mellitus with diabetic cataract
2	44982	C10FE00	Type 2 diabetes mellitus with diabetic cataract
1	12736	C10F500	Type 2 diabetes mellitus with gangrene
2	63690	C10FR00	Type 2 diabetes mellitus with gastroparesis
1	46917	C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
1	61071	C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
1	32627	C10FN00	Type 2 diabetes mellitus with ketoacidosis
1	51756	C10FP00	Type 2 diabetes mellitus with ketoacidotic coma

2	62674	C10FA00	Type 2 diabetes mellitus with mononeuropathy
2	12640	C10FC00	Type 2 diabetes mellitus with nephropathy
2	24836	C109C12	Type 2 diabetes mellitus with nephropathy
2	45919	C109212	Type 2 diabetes mellitus with neurological complications
2	34268	C10F200	Type 2 diabetes mellitus with neurological complications
2	35385	C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
2	66965	C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
2	47321	C10F100	Type 2 diabetes mellitus with ophthalmic complications
2	70316	C109112	Type 2 diabetes mellitus with ophthalmic complications
1	60699	C109F12	Type 2 diabetes mellitus with peripheral angiopathy
1	37806	C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
1	18390	C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
1	26054	C10FL00	Type 2 diabetes mellitus with persistent proteinuria
2	18425	C10FB00	Type 2 diabetes mellitus with polyneuropathy
2	18777	C10F000	Type 2 diabetes mellitus with renal complications
2	18209	C109012	Type 2 diabetes mellitus with renal complications
2	18496	C10F600	Type 2 diabetes mellitus with retinopathy
2	42762	C109612	Type 2 diabetes mellitus with retinopathy
1	49074	C10F400	Type 2 diabetes mellitus with ulcer
1	65704	C109412	Type 2 diabetes mellitus with ulcer
1	47954	C10F900	Type 2 diabetes mellitus without complication
1	24423	C108.13	Type I diabetes mellitus
1	12455	C10E.11	Type I diabetes mellitus
1	46850	C108811	Type I diabetes mellitus - poor control
1	63017	C108911	Type I diabetes mellitus maturity onset

2	17545	C108F11	Type I diabetes mellitus with diabetic cataract
1	42729	C108E11	Type I diabetes mellitus with hypoglycaemic coma
1	62209	C10EM11	Type I diabetes mellitus with ketoacidosis
1	66145	C10EN11	Type I diabetes mellitus with ketoacidotic coma
2	99231	C108B11	Type I diabetes mellitus with mononeuropathy
2	66872	C108D11	Type I diabetes mellitus with nephropathy
2	49146	C108211	Type I diabetes mellitus with neurological complications
2	61344	C108011	Type I diabetes mellitus with renal complications
2	38161	C108711	Type I diabetes mellitus with retinopathy
1	51957	C108511	Type I diabetes mellitus with ulcer
1	22884	C10F.11	Type II diabetes mellitus
1	18219	C109.13	Type II diabetes mellitus
1	24458	C109711	Type II diabetes mellitus - poor control
1	47315	C10F711	Type II diabetes mellitus - poor control
1	18143	C109G11	Type II diabetes mellitus with arthropathy
2	48192	C109E11	Type II diabetes mellitus with diabetic cataract
1	62107	C109511	Type II diabetes mellitus with gangrene
1	56268	C109D11	Type II diabetes mellitus with hypoglycaemic coma
2	50813	C109A11	Type II diabetes mellitus with mononeuropathy
2	64571	C109C11	Type II diabetes mellitus with nephropathy
2	102201	C10FC11	Type II diabetes mellitus with nephropathy
2	67905	C109211	Type II diabetes mellitus with neurological complications
2	47816	C109H11	Type II diabetes mellitus with neuropathic arthropathy
2	59725	C109111	Type II diabetes mellitus with ophthalmic complications
1	54899	C109F11	Type II diabetes mellitus with peripheral angiopathy

1	60796	C10FL11	Type II diabetes mellitus with persistent proteinuria
2	47409	C109B11	Type II diabetes mellitus with polyneuropathy
2	50527	C10FB11	Type II diabetes mellitus with polyneuropathy
2	50225	C109011	Type II diabetes mellitus with renal complications
2	57278	C10F011	Type II diabetes mellitus with renal complications
2	58604	C109611	Type II diabetes mellitus with retinopathy
2	49655	C10F611	Type II diabetes mellitus with retinopathy
1	55075	C109411	Type II diabetes mellitus with ulcer
1	43089	E004000	Uncomplicated arteriosclerotic dementia
1	42602	E001000	Uncomplicated presenile dementia
1	7323	E000.00	Uncomplicated senile dementia
1	28366	J12yy00	Unspec duodenal ulcer; unspec haemorrhage and/or perforation
1	94397	J11yy00	Unspec gastric ulcer; unspec haemorrhage and/or perforation
2	103353	B62z300	Unspec malig neop lymphoid/histiocytic intra-abdominal nodes
2	107638	B62z400	Unspec malig neop lymphoid/histiocytic lymph node axilla/arm
2	64427	B62z100	Unspec malig neop lymphoid/histiocytic lymph node head/neck
2	71609	B62z500	Unspec malig neop lymphoid/histiocytic nodes inguinal/leg
2	109342	B62z600	Unspec malig neop lymphoid/histiocytic of intrapelvic nodes
2	93384	B62z200	Unspec malig neop lymphoid/histiocytic of intrathoracic node
2	101465	B62z800	Unspec malig neop lymphoid/histiocytic of multiple sites
2	108037	B62z000	Unspec malig neop lymphoid/histiocytic of unspecified site
2	31794	B627W00	Unspecified B-cell non-Hodgkin's lymphoma

1	53669	J12y.00	Unspecified duodenal ulcer
1	65737	J12yz00	Unspecified duodenal ulcer NOS
1	93436	J12y300	Unspecified duodenal ulcer with haemorrhage and perforation
1	71904	J12y400	Unspecified duodenal ulcer with obstruction
1	657	J12y200	Unspecified duodenal ulcer with perforation
1	71150	J12y000	Unspecified duodenal ulcer without mention of complication
1	53081	J11y.00	Unspecified gastric ulcer
1	44284	J11yz00	Unspecified gastric ulcer NOS
1	57958	J11y100	Unspecified gastric ulcer with haemorrhage
1	73697	J11y400	Unspecified gastric ulcer with obstruction
1	36461	J11y200	Unspecified gastric ulcer with perforation
1	73338	J11y000	Unspecified gastric ulcer without mention of complication
1	63482	J14y.00	Unspecified gastrojejunal ulcer
1	66092	J14yz00	Unspecified gastrojejunal ulcer NOS
1	60346	J14y100	Unspecified gastrojejunal ulcer with haemorrhage
1	15979	J14y200	Unspecified gastrojejunal ulcer with perforation
1	50497	J13y.00	Unspecified peptic ulcer
1	60249	J13yz00	Unspecified peptic ulcer NOS
1	70456	J13y100	Unspecified peptic ulcer with haemorrhage
1	96622	J13y300	Unspecified peptic ulcer with haemorrhage and perforation
1	99670	J13y400	Unspecified peptic ulcer with obstruction
1	64111	J13y200	Unspecified peptic ulcer with perforation
1	67082	J13y000	Unspecified peptic ulcer without mention of complication
1	9013	66AJ.11	Unstable diabetes
1	54600	C10E412	Unstable insulin dependent diabetes mellitus

1	26855	C108400	Unstable insulin dependent diabetes mellitus
1	43921	C10E400	Unstable type 1 diabetes mellitus
1	60107	C108411	Unstable type I diabetes mellitus
1	12590	G58z.11	Weak heart
1	39478	H35y700	Wood asthma
1	100253	J615C00	Xanthomatous portal cirrhosis
1	51166	7A11311	Y graft abdominal Aortic aneurysm
1	92925	7A11211	Y graft of abdominal Aortic aneurysm (emergency)
1	4970	R054.00	[D]Gangrene
1	37750	R054z00	[D]Gangrene NOS
1	53634	R054200	[D]Gangrene of toe in diabetic
1	51634	R054000	[D]Gangrene, spreading cutaneous
1	31053	R054300	[D]Widespread diabetic foot gangrene
1	41271	ZV12C00	[V] Personal history of gastric ulcer
2	40561	ZV10711	[V]Personal history of Hodgkin's disease
2	36693	ZV10600	[V]Personal history of leukaemia
2	94597	ZV10611	[V]Personal history of lymphoid leukaemia
2	62814	ZV10000	[V]Personal history of malig neop of gastrointestinal tract
2	64568	ZV10012	[V]Personal history of malig neop of gastrointestinal tract
2	49289	ZV10100	[V]Personal history of malig neop of trachea/bronchus/lung
2	72262	ZV10200	[V]Personal history of malig neop other intrathoracic organ
2	12106	ZV10.00	[V]Personal history of malignant neoplasm
2	61655	ZV10211	[V]Personal history of malignant neoplasm - accessory sinus
2	68018	ZV10011	[V]Personal history of malignant neoplasm of anus
2	35816	ZV10511	[V]Personal history of malignant neoplasm of bladder

2	46282	ZV10y11	[V]Personal history of malignant neoplasm of bone
2	48085	ZV10y12	[V]Personal history of malignant neoplasm of brain
2	16639	ZV10300	[V]Personal history of malignant neoplasm of breast
2	32246	ZV10111	[V]Personal history of malignant neoplasm of bronchus
2	23936	ZV10411	[V]Personal history of malignant neoplasm of cervix uteri
2	103100	ZV10y13	[V]Personal history of malignant neoplasm of eye
2	109429	ZV10412	[V]Personal history of malignant neoplasm of genital organ
2	9444	ZV10400	[V]Personal history of malignant neoplasm of genital organ
2	28881	ZV10513	[V]Personal history of malignant neoplasm of kidney
2	47683	ZV10512	[V]Personal history of malignant neoplasm of kidney
2	57727	ZV10014	[V]Personal history of malignant neoplasm of large intestine
2	43311	ZV10212	[V]Personal history of malignant neoplasm of larynx
2	58177	ZV10015	[V]Personal history of malignant neoplasm of liver
2	29284	ZV10112	[V]Personal history of malignant neoplasm of lung
2	39863	ZV10214	[V]Personal history of malignant neoplasm of nose
2	51001	ZV10016	[V]Personal history of malignant neoplasm of oesophagus
2	52141	ZV10414	[V]Personal history of malignant neoplasm of ovary
2	37306	ZV10415	[V]Personal history of malignant neoplasm of prostate
2	62785	ZV10017	[V]Personal history of malignant neoplasm of rectum
2	47669	ZV10y14	[V]Personal history of malignant neoplasm of skin
2	49447	ZV10018	[V]Personal history of malignant neoplasm of stomach
2	48808	ZV10416	[V]Personal history of malignant neoplasm of testis
2	35771	ZV10y15	[V]Personal history of malignant neoplasm of thyroid
2	45803	ZV10y16	[V]Personal history of malignant neoplasm of tongue
2	99931	ZV10019	[V]Personal history of malignant neoplasm of tongue

2	30322	ZV10500	[V]Personal history of malignant neoplasm of urinary organ
2	46779	ZV10417	[V]Personal history of malignant neoplasm of uterine body
2	110058	ZV10613	[V]Personal history of myeloid leukaemia
2	66457	ZV10y00	[V]Personal history of other specified malignant neoplasm
1	26261	ZV12711	[V]Personal history of peptic ulcer
2	68612	ZV10z00	[V]Personal history of unspecified malignant neoplasm
2	72204	ZV10700	[V]Personal history other lymphatic/haematopoietic neoplasm
1	34944	Eu02z13	[X] Primary degenerative dementia NOS
1	4357	Eu02z14	[X] Senile dementia NOS
1	27759	Eu02z16	[X] Senile dementia, depressed or paranoid type
1	4693	Eu02z00	[X] Unspecified dementia
6	97091	ByuC500	[X]2ndry malignant neoplasm/bladder+oth+unsp urinary organs
6	68332	ByuC600	[X]2ndry malignant neoplasm/oth+unspec parts/nervous system
6	66163	ByuC200	[X]2ndry+unspcf malignant neoplasm lymph nodes/multi regions
2	60053	Byu..00	[X]Additional neoplasm classification terms
1	8195	Eu00z11	[X]Alzheimer's dementia unspec
1	102719	Gyu7200	[X]Aortic aneurysm of unspecified site, nonruptured
1	102725	Gyu7100	[X]Aortic aneurysm of unspecified site, ruptured
1	9565	Eu01.11	[X]Arteriosclerotic dementia
1	73901	Gyu6.00	[X]Cerebrovascular diseases
1	30706	Eu00200	[X]Dementia in Alzheimer's dis, atypical or mixed type
1	7664	Eu00.00	[X]Dementia in Alzheimer's disease

1	49263	Eu00000	[X]Dementia in Alzheimer's disease with early onset
1	38678	Eu00100	[X]Dementia in Alzheimer's disease with late onset
1	29386	Eu00z00	[X]Dementia in Alzheimer's disease, unspecified
1	12621	Eu02.00	[X]Dementia in other diseases classified elsewhere
1	64267	Eu02y00	[X]Dementia in other specified diseases classif elsewhere
1	52212	Cyu2.00	[X]Diabetes mellitus
2	64515	ByuDC00	[X]Diffuse non-Hodgkin's lymphoma, unspecified
6	96751	AyuCB00	[X]HIV disease result/haematological+immunologic abnorms,NEC
6	102117	AyuC300	[X]HIV disease resulting in multiple infections
6	69767	AyuC600	[X]HIV disease resulting in other non-Hodgkin's lymphoma
6	102252	AyuCC00	[X]HIV disease resulting in other specified conditions
6	107807	AyuC100	[X]HIV disease resulting in other viral infections
6	104134	AyuC400	[X]HIV disease resulting/other infectious+parasitic diseases
2	103532	K0A5500	[X]Heredtry nephrpthy NEC difus mesangiocapilry glomneph
6	62854	AyuC.00	[X]Human immunodeficiency virus disease
1	106515	Hyu4300	[X]Hypersensitivity pneumonitis due to other organic dusts
1	96630	Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
2	93665	Byu5300	[X]Kaposi's sarcoma, unspecified
1	26270	Eu02500	[X]Lewy body dementia
2	91896	Byu5800	[X]Mal neoplasm/connective+soft tissue of trunk,unspecified
2	105072	Byu5500	[X]Mal neoplasm/overlap les/periph nerv+autonomic nerv systm
2	47633	ByuA300	[X]Malig neopl, overlap lesion brain & other part of CNS
2	56925	Byu4000	[X]Malignant melanoma of other+unspecified parts of face
2	19444	Byu4100	[X]Malignant melanoma of skin, unspecified

2	99096	Byu2300	[X]Malignant neopl/overlapping les/resp+intrathoracic organs
2	40749	Byu3.00	[X]Malignant neoplasm of bone and articular cartilage
2	12499	Byu6.00	[X]Malignant neoplasm of breast
2	40595	Byu2000	[X]Malignant neoplasm of bronchus or lung, unspecified
2	35180	Byu1.00	[X]Malignant neoplasm of digestive organs
2	35285	ByuA.00	[X]Malignant neoplasm of eye, brain and other parts of cent
2	55588	Byu7300	[X]Malignant neoplasm of female genital organ, unspecified
2	40598	Byu7.00	[X]Malignant neoplasm of female genital organs
6	35186	ByuC.00	[X]Malignant neoplasm of ill-defined, secondary and unspeci
2	45766	Byu1200	[X]Malignant neoplasm of intestinal tract, part unspecified
2	58973	Byu0.00	[X]Malignant neoplasm of lip, oral cavity and pharynx
2	45262	Byu8200	[X]Malignant neoplasm of male genital organ, unspecified
2	40671	Byu8.00	[X]Malignant neoplasm of male genital organs
2	50292	Byu2500	[X]Malignant neoplasm of mediastinum, part unspecified
2	63925	ByuA200	[X]Malignant neoplasm of meninges, unspecified
2	40592	Byu5.00	[X]Malignant neoplasm of mesothelial and soft tissue
2	39027	ByuC000	[X]Malignant neoplasm of other specified sites
2	95671	Byu5700	[X]Malignant neoplasm of peritoneum, unspecified
2	35325	Byu2.00	[X]Malignant neoplasm of respiratory and intrathoracic orga
2	56121	Byu4300	[X]Malignant neoplasm of skin, unspecified
2	45260	Byu9000	[X]Malignant neoplasm of urinary organ, unspecified
2	35113	Byu9.00	[X]Malignant neoplasm of urinary tract
2	64497	Byu7000	[X]Malignant neoplasm of uterine adnexa, unspecified
2	60162	Byu5A00	[X]Malignant neoplasm overlapping lesion of skin

6 52029 ByuC800 [X]Malignant neoplasm without specification of site

2 43151 Byu3300 [X]Malignant neoplasm/bone+articular cartilage, unspecified

2 73296 Byu3100 [X]Malignant neoplasm/bones+articular cartilage/limb,unspfd

2 41515 ByuA100 [X]Malignant neoplasm/central nervous system, unspecified

2 91457 Byu5900 [X]Malignant neoplasm/connective + soft tissue,unspecified

2 86997 Byu2400 [X]Malignant neoplasm/ill-defined sites within resp system

2 68027 ByuA000 [X]Malignant neoplasm/other and unspecified cranial nerves

2 57756 Byu7100 [X]Malignant neoplasm/other specified female genital organs

2 57191 Byu8000 [X]Malignant neoplasm/other specified male genital organs

2 63300 Byu3200 [X]Malignant neoplasm/overlap lesion/bone+articulr cartilage

2 66444 Byu2100 [X]Malignant neoplasm/overlap lesion/heart,mediastinm+pleura

6 96226 ByuC100 [X]Malignant neoplasm/overlap lesion/other+ill-defined sites

2 101668 Byu5400 [X]Malignant neoplasm/peripheral nerves of trunk,unspecified

2 40740 ByuD.00 [X]Malignant neoplasms of lymphoid, haematopoietic and rela

2 63598 ByuE.00 [X]Malignant neoplasms/independent (primary) multiple sites

2 64897 ByuE000 [X]Malignant neoplasms/independent(primary)multiple sites

2 49292 Byu1300 [X]Malignant neoplsm/ill-defin sites within digestive system

2 19144 Byu4.00 [X]Melanoma and other malignant neoplasms of skin

2 21715 Byu5011 [X]Mesothelioma of lung

2 67034 Byu5000 [X]Mesothelioma of other sites

2 30526 Byu5100 [X]Mesothelioma, unspecified

1 31016 Eu01300 [X]Mixed cortical and subcortical vascular dementia

1	11175	Eu01100	[X]Multi-infarct dementia
2	7940	ByuDF11	[X]Non-Hodgkin's lymphoma NOS
2	8649	ByuDF00	[X]Non-Hodgkin's lymphoma, unspecified type
1	92036	Gyu6600	[X]Occlusion and stenosis of other cerebral arteries
1	90572	Gyu6500	[X]Occlusion and stenosis of other precerebral arteries
3	105611	Gyu9400	[X]Oesophageal varices in diseases classified elsewhere
2	109714	ByuDD00	[X]Oth and unspecif peripheral & cutaneous T-cell lymphomas
2	57184	Byu4200	[X]Oth malignant neoplasm/skin of oth+unspecfd parts of face
2	105025	ByuDA00	[X]Oth spcf mal neoplsm/lymphoid,haematopoietic+rltd tissue
2	43415	ByuD000	[X]Other Hodgkin's disease
2	53945	Kyu2000	[X]Other acute renal failure
1	6015	Jyu7100	[X]Other and unspecified cirrhosis of liver
2	53940	Kyu2100	[X]Other chronic renal failure
1	66058	Hyu3000	[X]Other emphysema
1	58706	Nyu4300	[X]Other forms of systemic lupus erythematosus
1	71763	Nyu4500	[X]Other forms of systemic sclerosis
1	53810	Gyu6200	[X]Other intracerebral haemorrhage
2	65165	ByuD900	[X]Other leukaemia of unspecified cell type
2	67029	ByuD500	[X]Other lymphoid leukaemia
2	102688	ByuD400	[X]Other malignant immunoproliferative diseases
2	89762	ByuD700	[X]Other monocytic leukaemia
2	61693	ByuD600	[X]Other myeloid leukaemia
1	93715	Nyu1100	[X]Other seropositive rheumatoid arthritis

2	43490	Byu1100	[X]Other specified carcinomas of liver
1	111096	Gyu6700	[X]Other specified cerebrovascular diseases
1	41686	Cyu2000	[X]Other specified diabetes mellitus
2	89329	ByuD800	[X]Other specified leukaemias
1	73961	Gyu7400	[X]Other specified peripheral vascular diseases
1	70221	Nyu1200	[X]Other specified rheumatoid arthritis
2	64336	ByuD300	[X]Other specified types of non-Hodgkin's lymphoma
1	65745	Gyu6100	[X]Other subarachnoid haemorrhage
2	98596	ByuD200	[X]Other types of diffuse non-Hodgkin's lymphoma
2	67518	ByuD100	[X]Other types of follicular non-Hodgkin's lymphoma
1	55313	Eu01y00	[X]Other vascular dementia
1	105939	Hyu4000	[X]Pneumoconiosis due to other dust containing silica
1	55838	Eu01111	[X]Predominantly cortical dementia
1	25704	Eu00011	[X]Presenile dementia,Alzheimer's type
1	43346	Eu00113	[X]Primary degen dementia of Alzheimer's type, senile onset
1	60059	Eu00012	[X]Primary degen dementia, Alzheimer's type, presenile onset
2	61930	Kyu2.00	[X]Renal failure
1	106440	Nyu1000	[X]Rheumatoid arthritis+involvement/other organs or systems
6	54253	ByuC700	[X]Secondary malignant neoplasm of other specified sites
6	57481	ByuC300	[X]Secondary malignant neoplasm/oth+unspc respiratory organs
6	88022	ByuC400	[X]Secondary malignant neoplasm/oth+unspcfd digestive organs
1	11379	Eu00112	[X]Senile dementia,Alzheimer's type
1	56202	Nyu1G00	[X]Seropositive rheumatoid arthritis, unspecified

1	108668	Gyu6000	[X]Subarachnoid haemorrhage from other intracranial arteries
1	8934	Eu01200	[X]Subcortical vascular dementia
2	63375	ByuDE00	[X]Unspecified B-cell non-Hodgkin's lymphoma
6	100769	AyuCD00	[X]Unspecified human immunodeficiency virus [HIV] disease
1	6578	Eu01.00	[X]Vascular dementia
1	46488	Eu01000	[X]Vascular dementia of acute onset
1	19393	Eu01z00	[X]Vascular dementia, unspecified

Appendix 5-1 *Campylobacter* and NTS Patients from CPRD and SGSS with a linked record in HES

	CPRD, 2000 -2015				PHE, 2009-2014			
	Salmonella		*Campylobacter*		*Salmonella*		*Campylobacter*	
	HES linked, N = 2,115	**CPRD only, N =608**	**HES linked, N = 13,960**	**CPRD only, N =3,878**	**Hes linked, N =17,093**	**Lab only, N = 25,891**	**Hes linked, N = 67,599**	**Lab only, N = 243,309**
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Age (years)								
Mean (Sd)	38 (18, 54)	36 (16, 55)	44.7 (21.2)	44.6 (21.1)	30.8 (22.4)	33.4 (25.6)	38.9 (20.4)	46.1 (23.3)
Sex								
Male	1,017 (48.1)	318 (52.3)	7,511 (53.8)	2,043 (52.7)	7,716 (45.1)	12,302 (47.5)	25,384 (37.6)	123,722 (50.8)
Female	1,098 (51.9)	290 (47.7)	6,449 (46.2)	1,835 (47.3)	8,882 (52.0)	13,337 (51.5)	41,245 (61.0)	119,195 (49.0)
Region								
North East	53 (2.5)	13 (2.1)	311 (2.2)	110 (2.8)	448 (2.6)	1,660 (6.4)	2,570 (3.8)	15,684 (6.4)
North West	276 (13.0)	69 (11.3)	2,109 (15.1)	434 (11.2)	1,344 (7.9)	3,880 (15.0)	6,321 (9.4)	31,552 (13.0)
Yorkshire & The Humber	74 (3.5)	41 (6.7)	509 (3.6)	188 (4.8)	1,331 (7.8)	3,194 (12.3)	6,535 (9.7)	27,434 (11.3)
East Midlands	83 (3.9)	60 (9.9)	399 (2.9)	357 (9.2)	6,73 (3.9)	2,419 (9.3)	4,400 (6.5)	20,237 (8.3)
West Midlands	210 (9.9)	32 (5.3)	1,730 (12.4)	241 (6.2)	1,208 (7.1)	2,503 (9.7)	7,130 (10.5)	26,692 (11.0)
East of England	281 (13.3)	60 (9.9)	1,854 (13.3)	293 (7.6)	2,292 (13.4)	2,454 (9.5)	9,411 (13.9)	27,035 (11.1)
London	299 (14.1)	89 (14.6)	1,216 (8.7)	345 (8.9)	4,716 (27.6)	2,999 (11.6)	9,265 (13.7)	18,646 (7.7)
South West	274 (13.0)	30 (4.9)	2,000 (14.3)	267 (6.9)	1,465 (8.6)	2,837 (11.0)	8,637 (12.8)	35,218 (14.5)
South East	221 (10.4)	86 (14.1)	1,662 (11.9)	666 (17.2)	3,616 (21.2)	3,945 (15.2)	13,330 (19.7)	40,811 (16.8)
South Central	344 (16.3)	128 (21.1)	2,170 (15.5)	977 (25.2)	-	-	-	-
Index of Multiple Deprivation (IMD)								
1-Least deprived	587 (27.8)	†	4189 (30.0)	†	2,920 (17.1)	5,668 (21.9)	8,309 (12.3)	37,776 (15.5)
2	494 (23.4)	†	3627 (26.0)	0 (0.0)	3,603 (21.1)	5,509 (21.3)	1,2769 (18.9)	43,688 (18.0)
3	436 (20.6)	0 (0.0)	2743 (19.6)	†	3,553 (20.8)	5,009 (19.3)	13,835 (20.5)	51,102 (21.0)

	CPRD, 2000 -2015				PHE, 2009-2014			
	Salmonella		*Campylobacter*		*Salmonella*		*Campylobacter*	
	HES linked, N = 2,115	**CPRD only, N =608**	**HES linked, N = 13,960**	**CPRD only, N =3,878**	**Hes linked, N =17,093**	**Lab only, N = 25,891**	**Hes linked, N = 67,599**	**Lab only, N = 243,309**
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
4	359 (17.0)	0 (0.0)	2107 (15.1)	†	4,133 (24.2)	5,141 (19.9)	16,636 (24.6)	54,658 (22.5)
5-Most deprived	237 (11.2)	0 (0.0)	1283 (9.2)	0 (0.0)	2,884 (16.9)	4,564 (17.6)	16,050 (23.7)	56,085 (23.1)
Missing	†	607 (99.8)	11 (0.1)	3874 (99.9)				
Travel abroad								
Yes	-	-	-	-	5,260 (30.8)	7,269 (28.1)	814 (1.2)	1,864 (0.8)
No	-	-	-	-	2,930 (17.1)	5,815 (22.5)	11,817 (17.5)	45,187 (18.6)
Unknown	-	-	-	-	8,903 (52.1)	12,807 (49.5)	54,968 (81.3)	196,258 (80.7)
Requesting organisation								
GP	-	-	-	-	317 (1.9)	1,141 (4.4)	42,133 (62.8)	136,342 (56.0)
A&E	-	-	-	-	16 (0.1)	52 (0.2)	793 (1.2)	3,245 (1.3)
Inpatients	-	-	-	-	12 (0.1)	232 (0.9)	1,983 (3.0)	18,985 (7.8)
Outpatients	-	-	-	-	28 (0.2)	103 (0.4)	1,715 (2.6)	6,337 (2.6)
Others	-	-	-	-	2 (<1)	2 (<1)	221 (0.3)	260 (0.1)
Unknown	-	-	-	-	16,705 (97.8)	24,361 (94.1)	20,275 (30.2)	78,140 (32.1)
CCI presence or absence								
No comorbidity	1559 (73.7)	420 (69.1)	9165 (65.7)	2535 (65.4)	-	-	-	-
1 or more CCI	556 (26.3)	188 (30.9)	4795 (34.3)	1343 (34.6)	-	-	-	-

Abbreviations and symbols: sd – Standard deviation; CCI – Charlson comorbidity index; - not applicable to data source; † events less than 5 not shown due to deductive disclosure in accordance with the ISAC protocol, where only category had events less than 5, a second category was also masked.

Appendix 5-2 *Campylobacter* and NTS patients with a previous history of the conditions of interest from CPRD, 2000-2015 and SGSS, 2009-2014

	CPRD, 2000-2015		SGSS, 2009-2014	
	NTS, N =150	Campylobacter, N =1126	NTS, N =527	Campylobacter, N =5,055
Age (years), mean (Sd)	44.1 (16.3)	48.1 (16.2)	46.1 (18.6)	51.7 (17.8)
Sex				
Male	41 (27.3)	354 (31.4)	212 (40.2)	2,457 (48.6)
Female	109 (72.7)	772 (68.6)	311 (59.0)	2,593 (51.3)
Unknown	-	-	4 (0.8)	5 (0.1)
IMD quintile				
1 - Least deprived	37 (24.7)	251 (22.3)	101 (19.2)	824 (16.3)
2	33 (22.0)	265 (23.5)	101 (19.2)	892 (17.6)
3	19 (12.7)	186 (16.5)	118 (22.4)	1,120 (22.2)
4	21 (14.0)	139 (12.3)	117 (22.2)	1,110 (22.0)
5 - Most deprived	16 (10.7)	66 (5.9)	90 (17.1)	1,109 (21.9)
missing	24 (16.0)	219 (19.4)	-	-
Conditions[1]				
ReA	†	†	36 (6.8)	298 (5.9)
IBS	112 (74.7%)	826 (73.4%)	85 (16.1)	1,001 (19.8)
GBS	0 (0.0%)	†	7 (1.3)	145 (2.9)
UC	17 (11.3%)	97 (8.6%)	268 (50.9)	2,304 (45.6)
CD	†	551 (4.9%)	153 (29.0)	1,384 (27.4)
RA	16 (10.7%)	132 (11.7%)	19 (3.6)	273 (5.4)
CCI presence or absence				
No comorbidity	83 (55.3)	657 (58.3)	-	-
1 or more CCI	67 (44.7)	469 (41.7)	-	-

Abbreviations and symbols: sd – Standard deviation; Conditions[1] – Some patients had a history of more than 1 condition of interest; ReA – Reactive arthritis; IBS – irritable bowel syndrome; GBS – Guillain-Barré syndrome; UC – ulcerative colitis; CD – Crohn's disease; RA – Rheumatoid arthritis; CCI – Charlson comorbidity index; - not applicable to data source; † events less than 5 not shown due to deductive disclosure in accordance with the ISAC protocol, where only category had events less than 5, a second category was also masked.

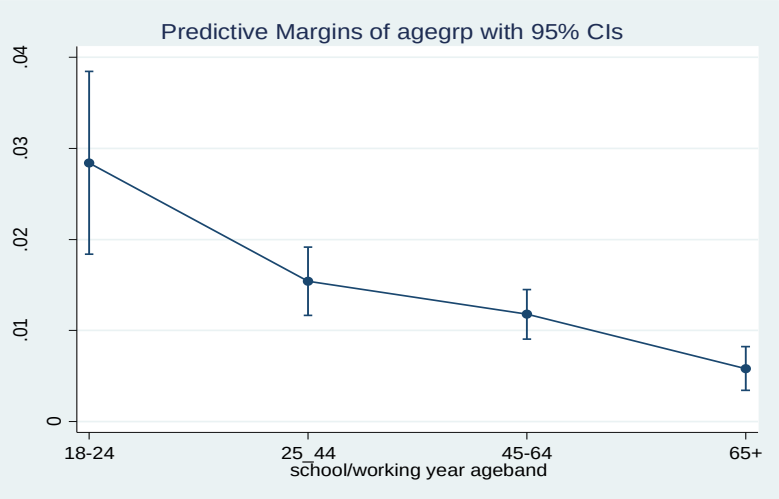
Appendix 6-1 Multivariate logistic regression on the use of PPI and onset of irritable bowel syndrome on Campylobacter patients with age (age groups recategorized)

Number of patients = 15,809

		Model *P*-value	***P* <0.001**		
Variable		aOR‡‡ IBS[1]	[95% Conf. Interval]		*P*-value
PPI		2.0	1.5	2.8	<0.001
Age (years)					
18-24	Referent				
25-44		0.5	0.3	0.8	0.003
45-64		0.4	0.3	0.6	<0.001
65+		0.2	0.1	0.4	<0.001
Sex					
Male	Referent				
Female		2.5	1.9	3.4	<0.001
Smoking status		1.1	0.9	1.3	0.318
CCI		0.9	0.7	1.3	0.698

Abbreviations and symbols: CCI - Charlson comorbidity index; ‡‡Adjusted odds ratio (adjusted for age, sex, smoking status and CCI); IBS[1]- 197 patients developed irritable bowel syndrome; 95% Confidence Interval; *P*-value likelihood ratio test

Appendix 6-1-2 Test for trend for the effect of patient's age on the risk of IBS amongst patients with a prescription for PPI within 12 months of *Campylobacter* infection



Contrast of marginal linear predictions, model *P*-value = *P* < 0.001				
Each age category against reference (18-24 years)	**Contrast**	**[95% Conf. Interval]**		***P*-value**
25-44 vs. 18-24	-0.63	-1.06	-0.21	0.004
45-64 vs. 18-24	-0.91	-1.35	-0.47	<0.001
65+ vs. 18-24	-1.61	-2.18	-1.04	<0.001
Each age category against adjacent category				
25-44 vs. 18-24	-0.63	-1.06	-0.21	0.004
45-64 vs. 25-44	-0.28	-0.62	0.07	0.113
65+ vs. 45-64	-0.70	-1.18	-0.23	0.004

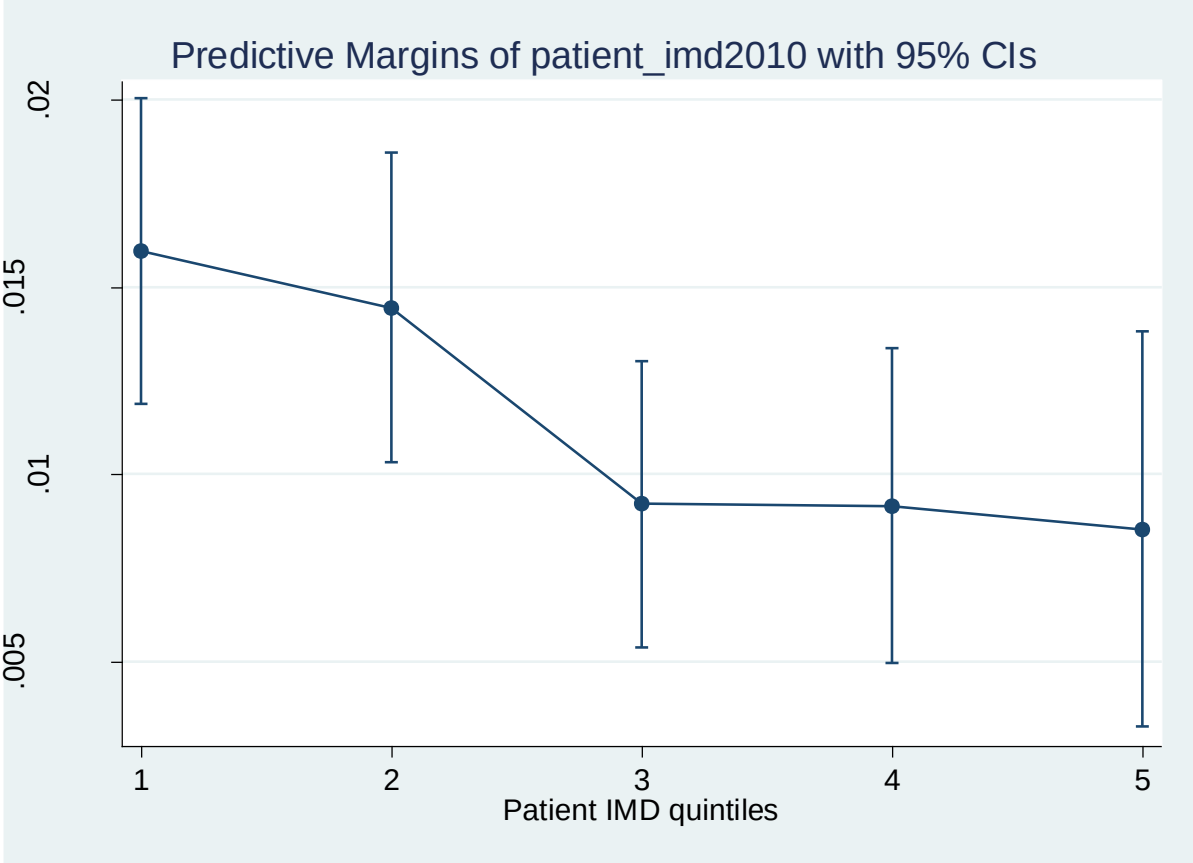
Appendix 6-2 Multivariate logistic regression on the use of PPI and onset of irritable bowel syndrome on Campylobacter patients with a linked record for IMD-2010

Appendix 6-2-1 shows the adjusted odds ratio (aOR) for the use of PPI and the onset of IBS amongst patients from England with a linked record for IMD-2010 who are aged 18 and over (n =12,358).

Sequelae	***Irritable bowel syndrome, n = 165***			
Model P-value	***P <0.001***			
	aOR	[95% Conf. Interval]		*P*-value
PPI	2.1	1.4	3.0	*P* <0.001
Agegroup				
18-24	Referent			
25-44	0.5	0.3	0.8	0.008
46-64	0.3	0.2	0.6	*P* <0.001
65+	0.2	0.1	0.3	*P* <0.001
Sex	2.3	1.6	3.2	*P* <0.001
CCI				
None	Referent			
1 or more	0.9	0.7	1.3	0.727
IMD				
1	Referent			
2	0.9	0.6	1.3	0.61
3	0.6	0.3	0.9	0.023
4	0.6	0.3	1.0	0.032
5	0.5	0.3	1.0	0.054

Abbreviations and symbols: PPI – proton pump inhibitor; CCI – Charlson comorbidity index; IMD – index of multiple deprivation; aOR -adjusted odds ratio (adjusted for age, sex and patient imd quintile); 95% Confidence Interval and *P*-value likelihood ratio test.

Appendix 6-2-2 Test for trend for the effect of patient's IMD-quintile on the risk of IBS amongst patients with a prescription for PPI within 12 months of *Campylobacter* infection

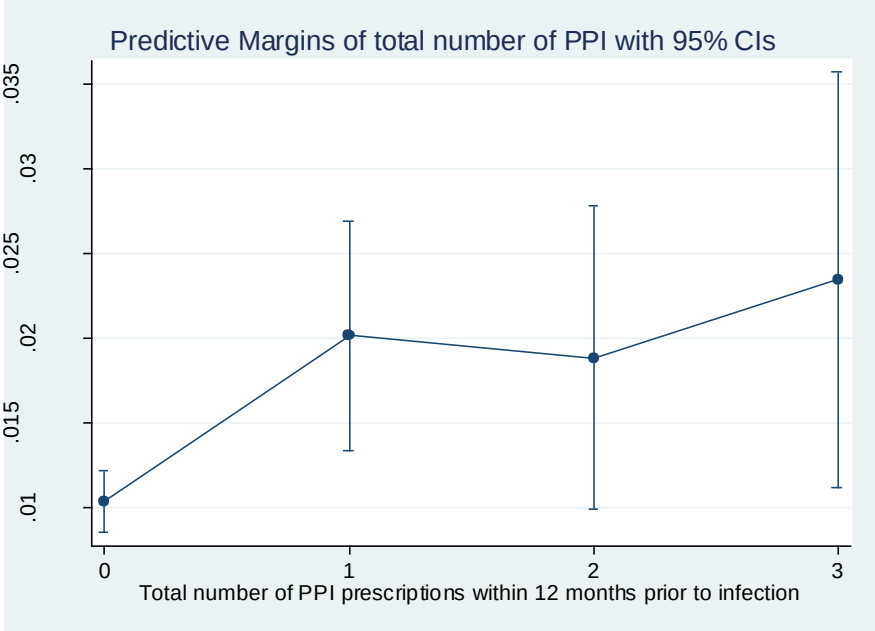


Contrast of marginal linear predictions, model *P*-value = 0.0492

Each IMD quintile against reference (IMD -1)	**Contrast**	**[95% Conf. Interval]**		***P*-value**
2 vs. 1	-0.10	-0.49	0.29	0.613
3 vs. 1	-0.56	-1.06	-0.06	0.027
4 vs. 1	-0.56	-1.10	-0.03	0.039
5 vs. 1	-0.64	-1.32	0.05	0.067
Each IMD quintile against adjacent quintile				
1 vs 2	0.10	0.20	-0.29	0.493
2 vs. 3	0.46	0.26	-0.05	0.971
3 vs. 4	0.01	0.32	-0.62	0.633
4 vs. 5	0.07	0.40	-0.71	0.850

Appendix 6-3 Test for trend for total number of proton pump inhibitors

Appendix 6-3-1 shows a possible linear trend from the fitted model treating PPI as a categorical variable based on the total number of prescriptions patients received in the 12 months prior to their GI infection.



Appendix 6-3-2 shows the marginal predictions for a test for trend, corresponding 95% confidence interval and the *P*-value of the likelihood ratio test

Contrast of marginal linear predictions, model *P*-value <0.001

Total PPI vs. Reference (None)	**Contrast**	**[95% Conf. Interval]**		***P*-value**
(1-5) vs. 0	0.68	0.29	1.07	0.001
(6-10) vs. 0	0.61	0.09	1.13	0.022
(> 10) vs. 0	0.83	0.26	1.41	0.005
Each Total PPI category against adjacent category				
0 vs. (1-5)	-0.68	-1.07	-0.29	0.001
(1-5) vs. (6-10)	0.07	-0.51	0.65	0.820
(6-10) vs. (>10)	-0.22	-0.92	0.47	0.528

Appendix 7-1 Consultation and staff type in CPRD

Appendix 7-1-1 Table of consultation type categories

CPRD code	Consultation type	Category by Hobbs et.*al* 2017	Category for thesis
1	Clinic	S	S
2	Night visit, Deputising service	O	VO
3	Follow-up/routine visit	V	VO
4	Night visit, Local rota	O	VO
5	Mail from patient	A	A
6	Night visit , practice	V	VO
7	Out of hours, Practice	O	VO
8	Out of hours, Non Practice	O	VO
9	Surgery consultation	S	S
10	Telephone call from a patient	T	T
11	Acute visit	V	V
12	Discharge details	A	A
13	Letter from Outpatients	A	A
14	Repeat Issue	A	A
15	Other	A	A
16	Results recording	A	A
17	Mail to patient	A	A
18	Emergency Consultation	S	S
19	Administration	A	A
20	Casualty Attendance	O	O
21	Telephone call to a patient	T	T
22	Third Party Consultation	A	A
23	Hospital Admission	O	O
24	Children's Home Visit	V	VO
25	Day Case Report	A	A
26	GOS18 Report	A	A
27	Home Visit	V	VO
28	Hotel Visit	V	VO
29	NHS Direct Report	A	A
30	Nursing Home Visit	V	VO
31	Residential Home Visit	V	VO
32	Twilight Visit	V	VO
33	Triage	T	T
34	Walk-in Centre	O	VO
35	Co-op Telephone advice	O	VO
36	Co-op Surgery Consultation	O	VO
37	Co-op Home Visit	O	VO
38	Minor Injury Service	O	O

CPRD code	Consultation type	Category by Hobbs et.*al* 2017	Category for thesis
39	Medicine Management	A	A
40	Community Clinic	O	O
43	Data Transferred from other system	A	A
46	Health Visitor Report	A	A
47	Hospital Inpatient Report	A	A
50	Night Visit	O	VO
52	Radiology Result	A	A
53	Referral Letter	A	A
55	Telephone Consultation	T	T
57	GP to GP communication transaction	A	A
58	Non-consultation medication data	A	A
59	Non-consultation data	A	A
60	ePharmacy message	A	A

Appendix 7-1-2 Table of staff type categories

CPRD code	Staff type	Category by Hobbs et.*al* 2017	Category for thesis
1	Senior Partner	G	G
2	Partner	G	G
10	Sole Practitioner	G	G
47	Salaried Partner	G	G
3	Assistant	G	G
4	Associate	G	G
5	Non-commercial local rota of less than 10 GPs	G	G
6	Commercial Deputising service	G	G
7	Locum	G	G
8	GP Registrar	G	G
50	GP Retainer	G	G
58	Other Additional Clinical Services	O	O
11	Practice Nurse	N	N
12	Health Visitor	O	N
13	Community Nurse	N	N
14	Midwife	O	N
15	Community Psychiatric Nurse	O	N
26	Physiotherapist	O	N
27	Chiropodist	O	N
28	Dentist	O	N
29	Dietician	O	N
30	Counsellor	O	N
31	Osteopath	O	N
33	Other Health Care Professional	O	N
34	Hospital Nurse	O	N
36	School Nurse	O	N
37	Health Education Officer	O	N
38	Contact Tracing Nurse	O	N
39	Stomatherapist	O	N
42	Chiropractor	O	N
43	Acupuncturist	O	N
44	Homeopath	O	N
45	Mental Handicap Nurse	O	N
48	Occupational Therapist	O	N
49	Speech Therapist	O	N
51	Phlebotomist	O	N
52	Other Medical & Dental	O	N
53	Other Students	O	O
54	Other Nursing & Midwifery	O	N
55	Other Allied Health Professionals	O	N
56	Other Professional Scientific & Technical	O	N
57	Other Healthcare Scientists	O	N
19	Non-qualified Dispenser	O	O
20	Practice Manager	A	A
21	Fund Manager	A	A
22	Business Manager	A	A
23	Administrator	A	A
24	Secretary	A	A
25	Receptionist	A	A
32	Maintenance staff	A	A

CPRD code	Staff type	Category by Hobbs et.*al* 2017	Category for thesis
40	Computer Manager	A	A
41	Interpreter/Link Worker	O	O
59	Other Admin & Clerical	A	A
60	Clinical Practitioner Access Role	O	O
61	Nurse Access Role	O	O
62	Nurse Manager Access Role	O	O
63	Health Professional Access Role	O	O
64	Healthcare Student Access Role	O	O
65	Biomedical Scientist Access Role	O	O
66	Clinical Coder Access Role	A	A
17	Pharmacist	O	O
18	Dispenser	O	O
9	Consultant	O	O
16	Social Worker	O	O
35	Community Medical Officer	O	O
67	Optometrist	O	O
68	Radiographer	O	O
0	Data Not Entered		
46	Carer		O

Key: A- Administration, G-General Practioner, N- Nurse, O-Other. All other categories were excluded from the analysis.

Appendix 7-2 Unit costs applied to primary care resource use

Resource	Unit cost (£)	Source	Notes
Consultations			
Consultation in surgery	GP - £32.30 (per 9.22 min consultation) Nurse - £7 (per 9.72 min consultation)	Unit Costs of Health and Social Care 2014. PSSRU [182]. Consultation duration[132]	Table 10.3b General Practitioner. Cost including qualifications, excluding direct staff costs: £41 per 11.7 min consultation including travel. Table 10.6 Nurse (GP Practice) - Cost per hour including qualifications: £43
GP consultation by telephone	£19.28 (per 5.4 min consultation)	Unit Costs of Health and Social Care 2014. PSSRU	Table 10.3b General Practitioner. Cost including qualifications, excluding direct staff costs: £25 per 7 min consultation excluding travel.

Resource	Unit cost (£)	Source	Notes
Consultation at home/out-of-hours	GP - £122.20 Nurse - £22.63	Unit Costs of Health and Social Care 2010. PSSRU [182] Hospital and community health services pay and price inflation index (HCHS) 2015/2016.	PSSRU: Table 10.6 Nurse (GP Practice). Cost including travel: £20 Table 10.8b General Practitioner. Cost including qualifications and travel, excluding direct staff costs: £108 HCHS: Inflation multiplier for 2014/2015 (0.8838)
Tests			
Clinical biochemistry	£1	NHS reference costs 2014/15 [183].	Main Schedule of Reference Costs Spreadsheet. Tab: Direct Access Pathology Services Service code: DAPS04

Resource	Unit cost (£)	Source	Notes
			Average cost
Cytology	£7	NHS reference costs 2014/15 [183].	
Histology	£29	NHS reference costs 2014/15 [183].	
Immunology	£5	NHS reference costs 2014/15 [183].	
Diagnostic Imaging	£87.62	NHS reference costs 2014/15 [183].	
Diagnostic Tests	£31.61	NHS reference costs 2014/15 [183].	
Haematology	£3	NHS reference costs 2014/15 [183].	Main Schedule of Reference Costs Spreadsheet. Tab: Direct Access Pathology Services Service code: DAPS05 Average cost
Microbiology	£7	NHS reference costs 2014/15 [183].	Main Schedule of Reference Costs Spreadsheet. Tab: Direct Access Pathology Services

Resource	Unit cost (£)	Source	Notes
			Service code: DAPS07 Average cost
Other Pathology tests		NHS reference costs 2014/15 [183].	
Prescriptions			
Prescriptions by British National Formulary (BNF) category:			
BNF 01: Gastrointestinal system	£5.35	NHS Digital PCA 2014/2015 [126].	TAB: Totals for BNF chapters – NIC/PXs (£)
BNF paragraph 1.3.5.0: Proton Pump Inhibitors	£2.19	NHS Digital PCA 2014/2015 [126].	TAB: Totals for BNF 1.3.5.0 (NIC Per Item)
BNF 02: Cardiovascular system	£3.20	NHS Digital PCA 2014/2015 [126].	TAB: Totals for BNF chapters – NIC/PXs (£)
BNF 03: Respiratory system	£16.15	NHS Digital PCA 2014/2015 [126].	TAB: Totals for BNF chapters – NIC/PXs (£)
BNF 04: Central nervous system	£9.58	NHS Digital PCA 2014/2015 [126].	TAB: Totals for BNF chapters – NIC/PXs (£)

Resource	Unit cost (£)	Source	Notes
BNF 05: Infections	£4.85	NHS Digital PCA 2014/2015 [126].	TAB: Totals for BNF chapters – NIC/PXs (£)
BNF paragraph 5.1.2.1: Cephalosporins	£3.02	NHS Digital PCA 2014/2015 [126].	TAB: Totals for BNF 5.1.2.1 (NIC Per Item)
BNF paragraph 5.1.5.0: Macrolides	£5.55	NHS Digital PCA 2014/2015 [126].	TAB: Totals for BNF 5.1.5.0 (NIC Per Item)
BNF paragraph 05.1.12.0: Quinolones	£5.15	NHS Digital PCA 2014/2015 [126].	TAB: Totals for BNF 5.1.12.0 (NIC Per Item)
BNF 06: Endocrine system	£12.29	NHS Digital PCA 2014/2015 [126].	TAB: Totals for BNF chapters – NIC/PXs (£)
BNF 07: Obstetrics, gynaecology, & urinary-tract disorders	£12.83	NHS Digital PCA 2014/2015 [126].	TAB: Totals for BNF chapters – NIC/PXs (£)
BNF 08: Malignant disease & immunosuppression	£53.51	NHS Digital PCA 2014/2015 [126].	TAB: Totals for BNF chapters – NIC/PXs (£)
BNF 09: Nutrition & blood	£11.36	NHS Digital PCA 2014/2015 [126].	TAB: Totals for BNF chapters – NIC/PXs (£)

Resource	Unit cost (£)	Source	Notes
BNF 10: Musculoskeletal & joint diseases	£6.37	NHS Digital PCA 2014/2015 [126].	TAB: Totals for BNF chapters – NIC/PXs (£)
BNF 11: Eye	£6.73	NHS Digital PCA 2014/2015 [126].	TAB: Totals for BNF chapters – NIC/PXs (£)
BNF 12: Ear, nose & oropharynx	£6.37	NHS Digital PCA 2014/2015 [126].	TAB: Totals for BNF chapters – NIC/PXs (£)
BNF 13: Skin	£7.38	NHS Digital PCA 2014/2015 [126].	TAB: Totals for BNF chapters – NIC/PXs (£)
BNF 14: Immunological products & vaccines	£8.68	NHS Digital PCA 2014/2015 [126].	TAB: Totals for BNF chapters – NIC/PXs (£)
BNF 15: Anaesthesia	£13.35	NHS Digital PCA 2014/2015 [126].	TAB: Totals for BNF chapters – NIC/PXs (£)
Miscellaneous	£22.13	NHS Digital PCA 2014/2015 [126].	TAB: Totals for BNF chapters – NIC/PXs (£)

Appendix 7-3 Laboratory and diagnostic tests grouping

Number	description	CPRD_category	Thesis_Category	Cost_Category
1	Bone studies	Biochemistry (Routine)	Bone profile*	Clinical Biochemistry
2	Calcium	Biochemistry (Routine)	Bone profile*	Clinical Biochemistry
3	Calcium adjusted	Biochemistry (Routine)	Bone profile*	Clinical Biochemistry
4	Female sex hormone profile	Biochemistry (Hormone)	Clinical Biochemistry	Clinical Biochemistry
5	Male sex hormone profile	Biochemistry (Hormone)	Clinical Biochemistry	Clinical Biochemistry
6	Gonadotrophin	Biochemistry (Hormone)	Clinical Biochemistry	Clinical Biochemistry
7	Follicle stimulating hormone	Biochemistry (Hormone)	Clinical Biochemistry	Clinical Biochemistry
8	Human chorionic gonadotropin	Biochemistry (Hormone)	Clinical Biochemistry	Clinical Biochemistry
9	Luteinising hormone	Biochemistry (Hormone)	Clinical Biochemistry	Clinical Biochemistry
10	Oestrodiol level	Biochemistry (Hormone)	Clinical Biochemistry	Clinical Biochemistry
11	Progesterone	Biochemistry (Hormone)	Clinical Biochemistry	Clinical Biochemistry
12	Prolactin level	Biochemistry (Hormone)	Clinical Biochemistry	Clinical Biochemistry
13	Testosterone	Biochemistry (Hormone)	Clinical Biochemistry	Clinical Biochemistry
14	Prostate specific antigen	Biochemistry (Hormone)	Clinical Biochemistry	Clinical Biochemistry
15	Serum cortisol	Biochemistry (Hormone)	Clinical Biochemistry	Clinical Biochemistry
16	Sex hormone binding globulin	Biochemistry (Hormone)	Clinical Biochemistry	Clinical Biochemistry
17	E2 prostaglandin	Biochemistry (Hormone)	Clinical Biochemistry	Clinical Biochemistry
18	Feto-placental hormones	Biochemistry (Hormone)	Clinical Biochemistry	Clinical Biochemistry
19	Serum parathyroid hormone	Biochemistry (Hormone)	Clinical Biochemistry	Clinical Biochemistry
20	Gastrointestinal hormones	Biochemistry (Hormone)	Clinical Biochemistry	Clinical Biochemistry
21	Serum growth hormone	Biochemistry (Hormone)	Clinical Biochemistry	Clinical Biochemistry
22	Serum insulin	Biochemistry (Hormone)	Clinical Biochemistry	Clinical Biochemistry
23	Serum adrenaline	Biochemistry (Hormone)	Clinical Biochemistry	Clinical Biochemistry
24	Serum noradrenaline	Biochemistry (Hormone)	Clinical Biochemistry	Clinical Biochemistry
25	Serum aldosterone	Biochemistry (Hormone)	Clinical Biochemistry	Clinical Biochemistry

Number	description	CPRD_category	Thesis_Category	Cost_Category
26	Serum renin	Biochemistry (Hormone)	Clinical Biochemistry	Clinical Biochemistry
27	Serum adrenocorticotrophic hormone	Biochemistry (Hormone)	Clinical Biochemistry	Clinical Biochemistry
28	B12 & Folate level	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
29	Drug levels	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
30	Iron studies	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
31	Guthrie test	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
32	Chemical function tests	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
33	Iron kinetics	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
34	Toxicology	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
35	Other drug levels	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
36	Blood gases	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
37	Disaccharidase tolerance test	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
38	Biochemical screening tests	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
39	B12 levels	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
40	Carbemazepine	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
41	Digoxin blood level	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
42	Serum ferritin	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
43	Folate level	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
44	Lithium levels	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
45	Phenobarbitone	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
46	Phenytoin	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
47	Theophylline	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
48	Valproate	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
49	Amylase	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
50	Cardiac enzymes	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
51	Blood trace elements/vitamins	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
52	Free tri-iodothyronine	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
53	Free thyroxine	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
54	Serum iron tests	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry

Number	description	CPRD_category	Thesis_Category	Cost_Category
55	Tricyclics	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
56	Serum amino acids	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
57	Blood lead level	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
58	Blood alcohol level	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
59	Methotrexate	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
60	Enzymes/specific protein	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
61	Other biochemistry test	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
62	Serum paracetamol	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
63	Serum cyclosporin	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
64	Schilling test - b12 absorption	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
65	Serum lactate	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
66	Carboxyhaemoglobin	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
67	Serum amiodarone	Biochemistry (Other)	Clinical Biochemistry	Clinical Biochemistry
68	Glucose tolerance test	Biochemistry (Routine)	Clinical Biochemistry	Clinical Biochemistry
69	Urinalysis - Glucose	Biochemistry (Routine)	Clinical Biochemistry	Clinical Biochemistry
70	Urinalysis - Protein	Biochemistry (Routine)	Clinical Biochemistry	Clinical Biochemistry
71	Acid phosphatase	Biochemistry (Routine)	Clinical Biochemistry	Clinical Biochemistry
72	Creatine phosphokinase level	Biochemistry (Routine)	Clinical Biochemistry	Clinical Biochemistry
73	Creatinine clearance	Biochemistry (Routine)	Clinical Biochemistry	Clinical Biochemistry
74	Lactate dehydrogenase	Biochemistry (Routine)	Clinical Biochemistry	Clinical Biochemistry
75	Serum inorganic phosphate	Biochemistry (Routine)	Clinical Biochemistry	Clinical Biochemistry
76	Prostatic acid phosphatase	Biochemistry (Routine)	Clinical Biochemistry	Clinical Biochemistry
77	Total protein	Biochemistry (Routine)	Clinical Biochemistry	Clinical Biochemistry
78	HbA1c - diabetic control	Biochemistry (Routine)	Clinical Biochemistry	Clinical Biochemistry
79	Uric acid blood level	Biochemistry (Routine)	Clinical Biochemistry	Clinical Biochemistry
80	Serum osmolality	Biochemistry (Routine)	Clinical Biochemistry	Clinical Biochemistry
81	Serum globin	Biochemistry (Routine)	Clinical Biochemistry	Clinical Biochemistry
82	Urine biochemistry	Biochemistry (Routine)	Clinical Biochemistry	Clinical Biochemistry

Number	description	CPRD_category	Thesis_Category	Cost_Category
83	Total iron binding capacity	Biochemistry (Routine)	Clinical Biochemistry	Clinical Biochemistry
84	Fructosamine	Biochemistry (Routine)	Clinical Biochemistry	Clinical Biochemistry
85	Urine microalbumin	Biochemistry (Routine)	Clinical Biochemistry	Clinical Biochemistry
86	Anion gap	Biochemistry (Routine)	Clinical Biochemistry	Clinical Biochemistry
87	Glomerular Filtration Rate	Biochemistry (Routine)	Clinical Biochemistry	Clinical Biochemistry
88	Urine Leucocytes	Biochemistry (Routine)	Clinical Biochemistry	Clinical Biochemistry
89	Calculus examination	Microbiology	Clinical Biochemistry	Clinical Biochemistry
90	Urine cytology	Other Pathology Tests	Cytology	Cytology
91	Sputum cytology	Other Pathology Tests	Cytology	Cytology
92	Cervical cytology	Other Pathology Tests	Cytology	Cytology
93	Barium enema	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
94	Barium meal	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
95	Intravenous pyelogram (IVP)	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
96	Mammogram	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
97	Abdominal ultra sound	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
98	Pelvic ultra sound	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
99	Other diagnostic imaging	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
100	Ankle x-ray	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
101	Chest x-ray	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
102	Elbow x-ray	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
103	Upper leg x-ray	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
104	Foot x-ray	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
105	Hand x-ray	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
106	Hip x-ray	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
107	Upper arm x-ray	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
108	Knee x-ray	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
109	Neck x-ray	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
110	Pelvis x-ray	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
111	Ribs x-ray	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging

Number	description	CPRD_category	Thesis_Category	Cost_Category
112	Shoulder x-ray	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
113	Sinus x-ray	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
114	Skull x-ray	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
115	Spine x-ray	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
116	Lower leg x-ray	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
117	Wrist x-ray	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
118	Nuclear medicine	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
119	CAT scan	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
120	MRI scan	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
121	Carotid angiogram	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
122	Coronary angiogram	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
123	Femoral arteriogram	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
124	Barium swallow	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
125	Barium follow through	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
126	General ultra sound scan	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
127	Abdominal xray	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
128	Lower arm x-ray	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
129	Bone density studies	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
130	Venography	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
131	Renal arteriography	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
132	Fluoroscopy	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
133	Lymphangiography	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
134	Tomography	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
135	Sialogram	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
136	Abdominal aortogram	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
137	Dexa scan/bone mineral density	Diagnostic Imaging	Diagnostic Imaging	Diagnostic Imaging
138	Tactile Sensation	Diagnostic Tests	Diagnostic Tests	Diagnostic Tests
139	Scoring test result	Diagnostic Tests	Diagnostic Tests	Diagnostic Tests
140	ECG exercise	Diagnostic Tests	Diagnostic Tests	Diagnostic Tests

Number	description	CPRD_category	Thesis_Category	Cost_Category
141	Nerve conduction studies	Diagnostic Tests	Diagnostic Tests	Diagnostic Tests
142	Doppler ultrasound peripheral pulse	Diagnostic Tests	Diagnostic Tests	Diagnostic Tests
143	ECG ambulatory	Diagnostic Tests	Diagnostic Tests	Diagnostic Tests
144	Pulmonary function tests	Diagnostic Tests	Diagnostic Tests	Diagnostic Tests
145	Ambulatory blood pressure	Diagnostic Tests	Diagnostic Tests	Diagnostic Tests
146	Skin prick test	Diagnostic Tests	Diagnostic Tests	Diagnostic Tests
147	Electroencephalography	Diagnostic Tests	Diagnostic Tests	Diagnostic Tests
148	Oesophagoscopy	Diagnostic Tests	Diagnostic Tests	Diagnostic Tests
149	Echocardiogram	Diagnostic Tests	Diagnostic Tests	Diagnostic Tests
150	Transfer coefficient for CO	Diagnostic Tests	Diagnostic Tests	Diagnostic Tests
151	Intraocular pressure left	Diagnostic Tests	Diagnostic Tests	Diagnostic Tests
152	Intraocular pressure right	Diagnostic Tests	Diagnostic Tests	Diagnostic Tests
153	Pulse oximetry	Diagnostic Tests	Diagnostic Tests	Diagnostic Tests
154	Serum chloride	Biochemistry (Routine)	Electrolytes*	Clinical Biochemistry
155	Serum creatinine	Biochemistry (Routine)	Electrolytes*	Clinical Biochemistry
156	Blood glucose	Biochemistry (Routine)	Electrolytes*	Clinical Biochemistry
157	Fasting glucose	Biochemistry (Routine)	Electrolytes*	Clinical Biochemistry
158	Serum electrolytes	Biochemistry (Routine)	Electrolytes*	Clinical Biochemistry
159	Endoscopy	Diagnostic Tests	Endoscopy*	Diagnostic Tests
160	Bronchoscopy	Diagnostic Tests	Endoscopy*	Diagnostic Tests
161	Duodenoscopy	Diagnostic Tests	Endoscopy*	Diagnostic Tests
162	Colonoscopy	Diagnostic Tests	Endoscopy*	Diagnostic Tests
163	Sigmoidoscopy	Diagnostic Tests	Endoscopy*	Diagnostic Tests
164	Blood lipids	Biochemistry (Routine)	Fats*	Clinical Biochemistry
165	Lipoprotein electrophoresis	Biochemistry (Routine)	Fats*	Clinical Biochemistry
166	Serum cholesterol	Biochemistry (Routine)	Fats*	Clinical Biochemistry
167	High density lipoprotein	Biochemistry (Routine)	Fats*	Clinical Biochemistry
168	Low density lipoprotein	Biochemistry (Routine)	Fats*	Clinical Biochemistry

Number	description	CPRD_category	Thesis_Category	Cost_Category
169	Triglycerides	Biochemistry (Routine)	Fats*	Clinical Biochemistry
170	Very low density lipoprotein	Biochemistry (Routine)	Fats*	Clinical Biochemistry
171	HDL/LDL ratio	Biochemistry (Routine)	Fats*	Clinical Biochemistry
172	Full blood count	Haematology	Full blood count*	Clinical Biochemistry
173	Differential white cell count	Haematology	Full blood count*	Clinical Biochemistry
174	Eosinophil count	Haematology	Full blood count*	Clinical Biochemistry
175	Haemoglobin	Haematology	Full blood count*	Clinical Biochemistry
176	Monocyte count	Haematology	Full blood count*	Clinical Biochemistry
177	Neutrophil count	Haematology	Full blood count*	Clinical Biochemistry
178	Platelets	Haematology	Full blood count*	Clinical Biochemistry
179	Red blood cell count	Haematology	Full blood count*	Clinical Biochemistry
180	Lymphocyte count	Haematology	Full blood count*	Clinical Biochemistry
181	Packed cell volume	Haematology	Full blood count*	Clinical Biochemistry
182	Basophil count	Haematology	Full blood count*	Clinical Biochemistry
183	RBC red blood cell size	Haematology	Full blood count*	Clinical Biochemistry
184	PF best ever	Asthma	GP does in surgery*	Exclude
185	PF predicted	Asthma	GP does in surgery*	Exclude
186	PF current	Asthma	GP does in surgery*	Exclude
187	Urine dipstick for glucose	Biochemistry (Routine)	GP does in surgery*	Exclude
188	Urine dipstick for protein	Biochemistry (Routine)	GP does in surgery*	Exclude
189	Urine dipstick for ketones	Biochemistry (Routine)	GP does in surgery*	Exclude
190	Urine dipstick for blood	Biochemistry (Routine)	GP does in surgery*	Exclude
191	Urine dipstick for ph	Biochemistry (Routine)	GP does in surgery*	Exclude
192	Urine dipstick for nitrites	Biochemistry (Routine)	GP does in surgery*	Exclude
193	Electrocardiogram	Diagnostic Tests	GP does in surgery*	Exclude
194	Forced expiration volume in 1 sec	Diagnostic Tests	GP does in surgery*	Exclude
195	FEV1 / FVC	Diagnostic Tests	GP does in surgery*	Exclude
196	Forced vital capacity	Diagnostic Tests	GP does in surgery*	Exclude
197	Airway reversibility	Diagnostic Tests	GP does in surgery*	Exclude
198	Total lung capacity	Diagnostic Tests	GP does in surgery*	Exclude
199	Spirometry	Diagnostic Tests	GP does in surgery*	Exclude
200	Lung function post steriods	Diagnostic Tests	GP does in surgery*	Exclude
201	Lung function pre-steroids	Diagnostic Tests	GP does in surgery*	Exclude
202	Height	Examination Findings	GP does in surgery*	Exclude
203	Fundoscopy	Examination Findings	GP does in surgery*	Exclude
204	Target blood pressure	Examination Findings	GP does in surgery*	Exclude

Number	description	CPRD_category	Thesis_Category	Cost_Category
205	Weight	Examination Findings	GP does in surgery*	Exclude
206	Peripheral oedema	Examination Findings	GP does in surgery*	Exclude
207	Heart examination	Examination Findings	GP does in surgery*	Exclude
208	Blood pressure	Examination Findings	GP does in surgery*	Exclude
209	Jugular venous pressure	Examination Findings	GP does in surgery*	Exclude
210	Respiratory rate	Examination Findings	GP does in surgery*	Exclude
211	Temperature	Examination Findings	GP does in surgery*	Exclude
212	Postural drop in BP	Examination Findings	GP does in surgery*	Exclude
213	Faecal occult blood	Microbiology	GP does in surgery*	Exclude
214	Blood group	Haematology	Haematology*	Haematology
215	Clotting tests	Haematology	Haematology*	Haematology
216	Blood group antibodies	Haematology	Haematology*	Haematology
217	Film report	Haematology	Haematology*	Haematology
218	Bone marrow examination	Haematology	Haematology*	Haematology
219	Colour index	Haematology	Haematology*	Haematology
220	Microscopy for malarial parasites	Haematology	Haematology*	Haematology
221	Red blood cell shape	Haematology	Haematology*	Haematology
222	Red blood cell colour	Haematology	Haematology*	Haematology
223	Haemoglobin variants	Haematology	Haematology*	Haematology
224	Red blood cell clumping	Haematology	Haematology*	Haematology
225	Red blood cells enzymes	Haematology	Haematology*	Haematology
226	Sickle cell disease screen	Haematology	Haematology*	Haematology
227	Haematology screening tests	Haematology	Haematology*	Haematology
228	Mean corpuscular haemoglobin	Haematology	Haematology*	Haematology
229	MCH Hb Concentration	Haematology	Haematology*	Haematology
230	Mean corpuscular volume	Haematology	Haematology*	Haematology
231	Reticulocytes	Haematology	Haematology*	Haematology
232	Total White Blood cell count	Haematology	Haematology*	Haematology
233	Erythrocyte sedimentation rate	Haematology	Haematology*	Haematology
234	Large unstained cells	Haematology	Haematology*	Haematology
235	Prothrombin time	Haematology	Haematology*	Haematology
236	Partial thromboplastin time	Haematology	Haematology*	Haematology
237	INR	Haematology	Haematology*	Haematology
238	RBC - folate	Haematology	Haematology*	Haematology
239	Plasma viscosity	Haematology	Haematology*	Haematology
240	Serum fibrinogen level	Haematology	Haematology*	Haematology
241	Thrombin time	Haematology	Haematology*	Haematology

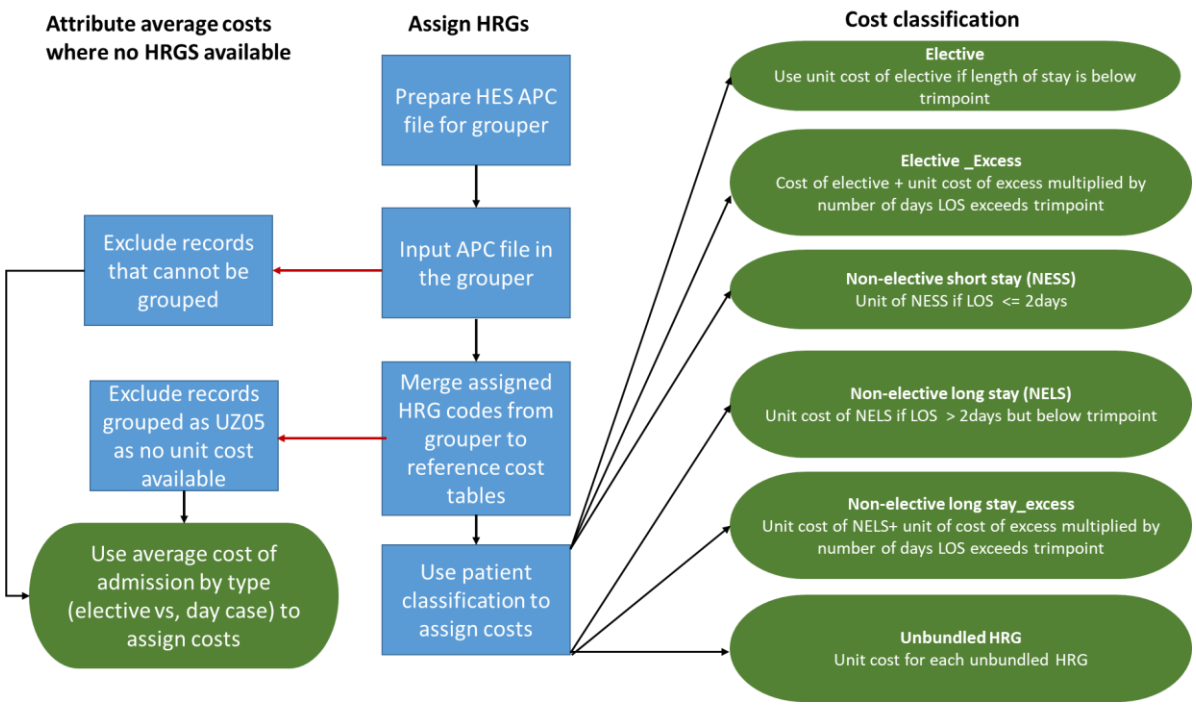
Number	description	CPRD_category	Thesis_Category	Cost_Category
242	Histology	Other Pathology Tests	Histology	Histology
243	Glandular fever test	Serology & Immunology	Immunology	Immunology
244	Serology	Serology & Immunology	Immunology	Immunology
245	Rubella test	Serology & Immunology	Immunology	Immunology
246	Tuberculin test	Serology & Immunology	Immunology	Immunology
247	Anti mitochondrial antibodies	Serology & Immunology	Immunology	Immunology
248	Anti nuclear antibodies	Serology & Immunology	Immunology	Immunology
249	Syphilis test	Serology & Immunology	Immunology	Immunology
250	Viral studies	Serology & Immunology	Immunology	Immunology
251	Plasma electrophoresis	Serology & Immunology	Immunology	Immunology
252	SH-antigen (hepatitis b) test	Serology & Immunology	Immunology	Immunology
253	HIV test	Serology & Immunology	Immunology	Immunology
254	Infection titres	Serology & Immunology	Immunology	Immunology
255	Anti smooth muscle autoantibodies	Serology & Immunology	Immunology	Immunology
256	Thyroid autoantibodies	Serology & Immunology	Immunology	Immunology
257	DNA binding autoantibodies	Serology & Immunology	Immunology	Immunology
258	Other autoantibodies	Serology & Immunology	Immunology	Immunology
259	Hepatitis a test	Serology & Immunology	Immunology	Immunology
260	CAP (RAST)	Serology & Immunology	Immunology	Immunology
261	LE cells	Serology & Immunology	Immunology	Immunology
262	Other immunology tests	Serology & Immunology	Immunology	Immunology
263	Legionella antibody test	Serology & Immunology	Immunology	Immunology
264	Immuno electrophoresis	Serology & Immunology	Immunology	Immunology
265	HLA tissue typing	Serology & Immunology	Immunology	Immunology
266	Parietal cell autoantibodes	Serology & Immunology	Immunology	Immunology
267	Adrenal autoantibodies	Serology & Immunology	Immunology	Immunology

Number	description	CPRD_category	Thesis_Category	Cost_Category
268	C Reactive protein	Serology & Immunology	Immunology	Immunology
269	Immunoglobulin	Serology & Immunology	Immunology	Immunology
270	Rheumatoid factor	Serology & Immunology	Immunology	Immunology
271	Antostreptolysin o titre	Serology & Immunology	Immunology	Immunology
272	Complement tests	Serology & Immunology	Immunology	Immunology
273	Tumour markers	Serology & Immunology	Immunology	Immunology
274	Immunology screening tests	Serology & Immunology	Immunology	Immunology
275	Hepatitis B Antibody	Serology & Immunology	Immunology	Immunology
276	Liver function tests	Biochemistry (Routine)	Liver function tests*	Clinical Biochemistry
277	Liver enzymes	Biochemistry (Routine)	Liver function tests*	Clinical Biochemistry
278	Albumin	Biochemistry (Routine)	Liver function tests*	Clinical Biochemistry
279	Alkaline phosphatase	Biochemistry (Routine)	Liver function tests*	Clinical Biochemistry
280	Alanine aminotransferase	Biochemistry (Routine)	Liver function tests*	Clinical Biochemistry
281	Aspartate aminotransferase	Biochemistry (Routine)	Liver function tests*	Clinical Biochemistry
282	Bilirubin	Biochemistry (Routine)	Liver function tests*	Clinical Biochemistry
283	Gamma glutamyl transpeptidase	Biochemistry (Routine)	Liver function tests*	Clinical Biochemistry
284	Mid-stream specimen of urine	Microbiology	Microbiology	Microbiology
285	Nail clippings	Microbiology	Microbiology	Microbiology
286	Sputum culture	Microbiology	Microbiology	Microbiology
287	Stool culture	Microbiology	Microbiology	Microbiology
288	Urine test	Microbiology	Microbiology	Microbiology
289	Eye swab	Microbiology	Microbiology	Microbiology
290	Cervical swab	Microbiology	Microbiology	Microbiology
291	High vaginal swab	Microbiology	Microbiology	Microbiology
292	Nose swab	Microbiology	Microbiology	Microbiology
293	Other swab	Microbiology	Microbiology	Microbiology
294	Penile swab	Microbiology	Microbiology	Microbiology
295	Skin swab	Microbiology	Microbiology	Microbiology
296	Throat swab	Microbiology	Microbiology	Microbiology
297	Vaginal swab	Microbiology	Microbiology	Microbiology
298	Wound swab	Microbiology	Microbiology	Microbiology
299	Examination of faeces	Microbiology	Microbiology	Microbiology
300	Synovial fluid examination	Microbiology	Microbiology	Microbiology
301	Sputum examination	Microbiology	Microbiology	Microbiology

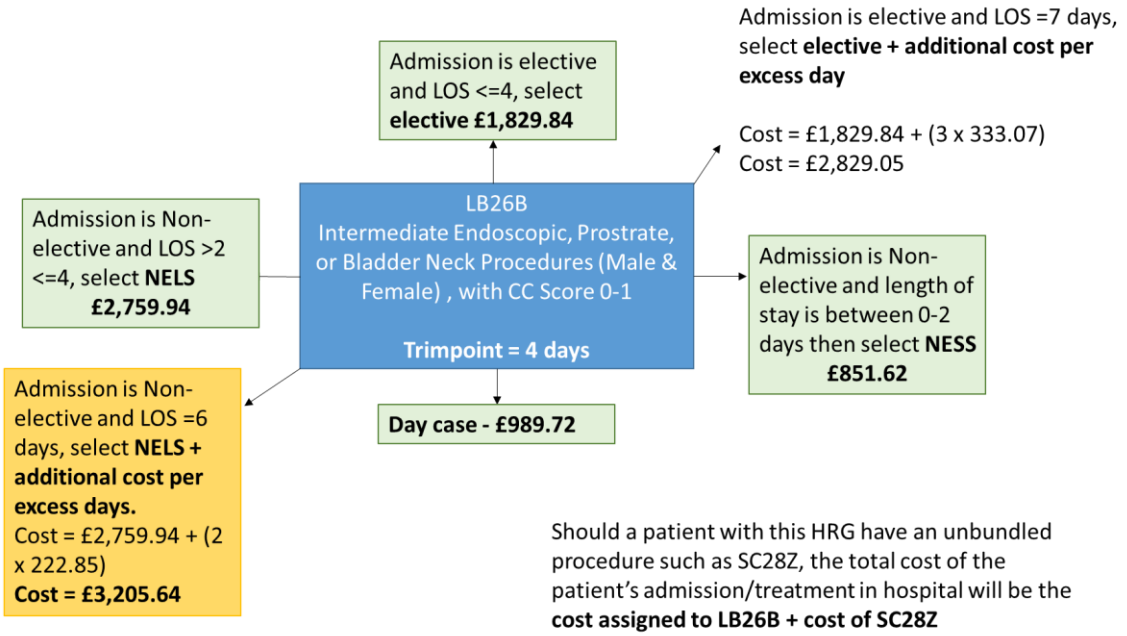
Number	description	CPRD_category	Thesis_Category	Cost_Category
302	Other bacteriology tests	Microbiology	Microbiology	Microbiology
303	Urethral swab	Microbiology	Microbiology	Microbiology
304	Vomit examination	Microbiology	Microbiology	Microbiology
305	Chlamydia	Microbiology	Microbiology	Microbiology
306	Cerebro-spinal fluid examination	Microbiology	Microbiology	Microbiology
307	Ascitic fluid examination	Microbiology	Microbiology	Microbiology
308	Microscopy culture & sensitivities	Microbiology	Microbiology	Microbiology
309	Pleural fluid examination	Microbiology	Microbiology	Microbiology
310	Ear swab	Microbiology	Microbiology	Microbiology
481	Other laboratory tests	Other Pathology Tests	Other_Pathology	Other_Pathology
482	Other Lab Result Information	Other Pathology Tests	Other_Pathology	Other_Pathology
483	Thyroid function	Biochemistry (Other)	Thyroid*	Clinical Biochemistry
484	Thyroxine	Biochemistry (Other)	Thyroid*	Clinical Biochemistry
485	Thyroid disorder screening	Biochemistry (Routine)	Thyroid*	Clinical Biochemistry
486	Triodothyronine	Biochemistry (Routine)	Thyroid*	Clinical Biochemistry
487	Thyroid disease	Disease Registers	Thyroid*	Clinical Biochemistry
488	Thyroid stimulating hormone	Biochemistry (Hormone)	Thyroid*	Clinical Biochemistry
489	Urea and electrolytes	Biochemistry (Routine)	Urea and Eelectrolytes*	Clinical Biochemistry
490	Potassium	Biochemistry (Routine)	Urea and Eelectrolytes*	Clinical Biochemistry
491	Sodium	Biochemistry (Routine)	Urea and Eelectrolytes*	Clinical Biochemistry
492	Urea - blood	Biochemistry (Routine)	Urea and Eelectrolytes*	Clinical Biochemistry
493	Serum bicarbonate	Biochemistry (Routine)	Urea and Eelectrolytes*	Clinical Biochemistry
494	Albumin creatinine ratio	Biochemistry (Routine)	Urea and Eelectrolytes*	Clinical Biochemistry

*Batch tests – 1 record per batch selected

Appendix 7-4-1 Assigning HRGs and attaching appropriate costs



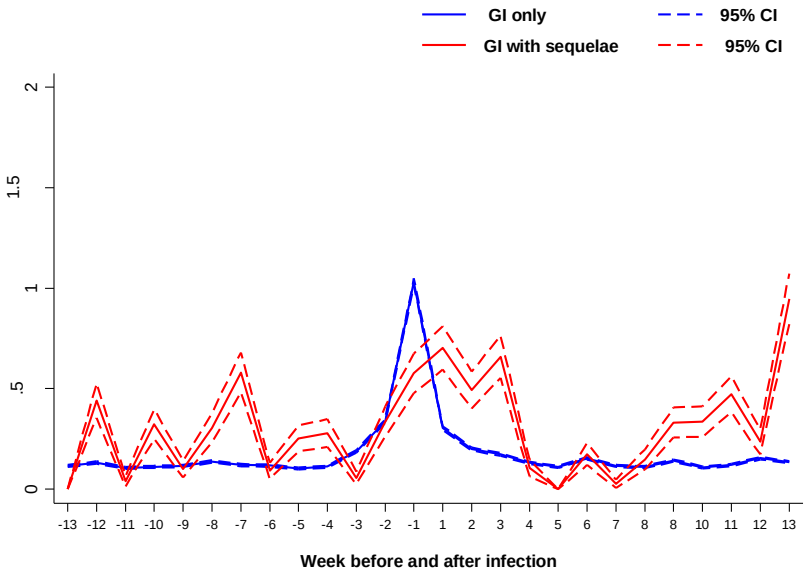
Appendix 7-4-2 Example for attaching appropriate costs to derived HRG



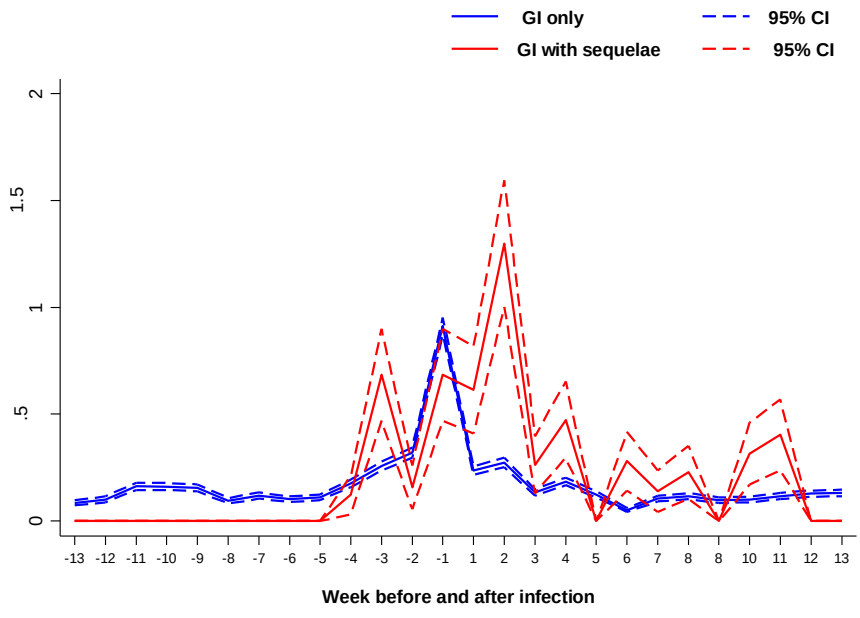
Should a patient with this HRG have an unbundled procedure such as SC28Z, the total cost of the patient's admission/treatment in hospital will be the **cost assigned to LB26B + cost of SC28Z**

Appendix 7-5 Weekly average number of consultations and tests per patient in the cohort

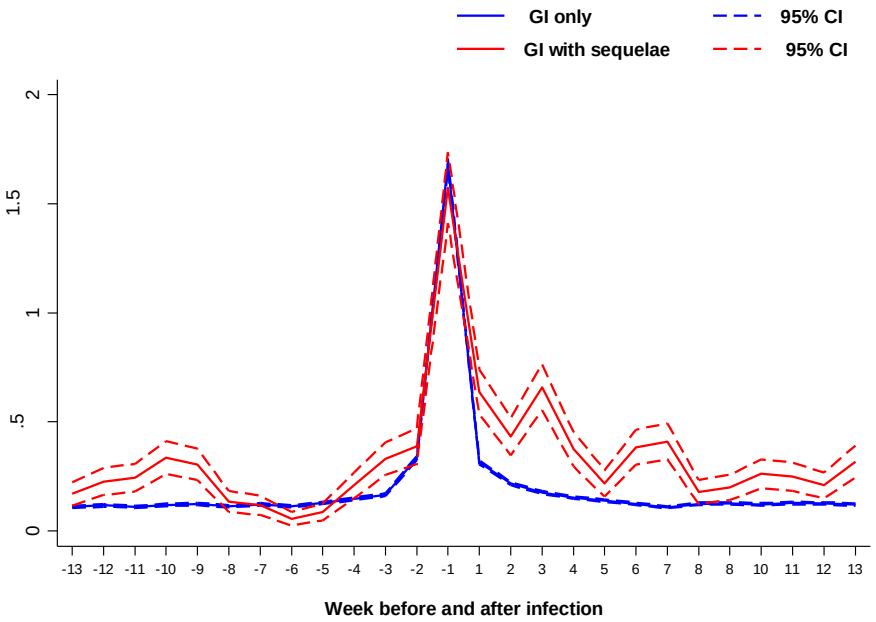
A - *Campylobacter* patients - Consultations



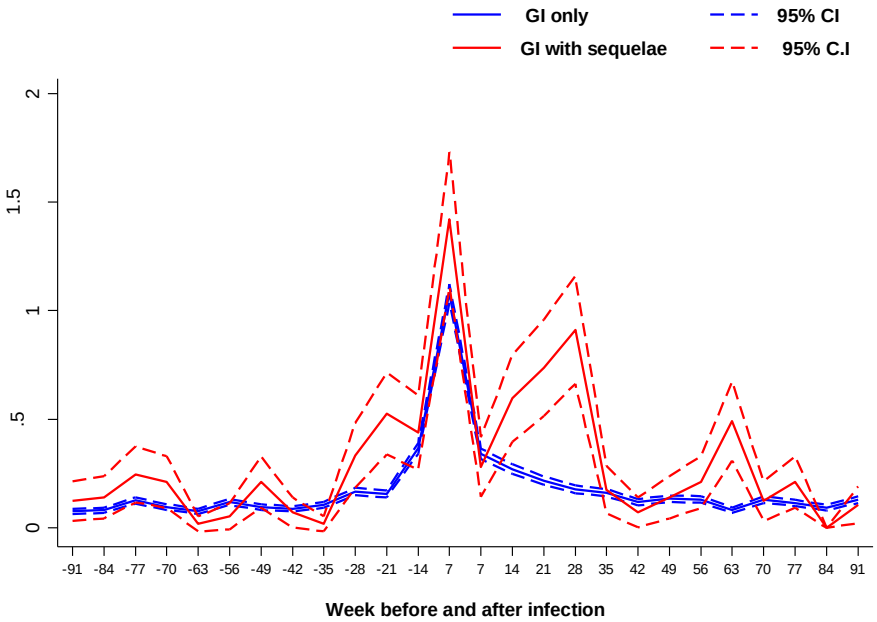
B - NTS patients – Consultations



C – *Campylobacter* patients – Tests



D – NTS patients – Tests



Appendix 7-6 Estimated mean total annual cost impact of sequelae of *Campylobacter* and NTS infection on the NHS in England

Step 1

Annual cost impact of sequelae per patient

	Cost impact per case per quarter	Cost impact per case per year
Campylobacter	£331	£1,324
NTS	£221	£884

Step 2

Number presenting to GP annually

	UK	lcl	ucl	England†	lcl	ucl
Campylobacter	78,973	55,486	112,401	63,178	44,389	89,921
NTS	11,291	4,649	27,418	9,033	3,719	21,934

Sequelae rate for England only	
Campylobacter	0.015
NTS	0.028

Expected number developing sequelae annually in England

	Number	lcl	ucl
Campylobacter	948	666	1,349
NTS	253	104	614

Step 3

The estimated mean total annual cost impact on NHS in England

	Total cost	lcl	ucl
Campylobacter	£1,254,723	£881,562	£1,785,827
NTS	£223,580	£92,058	£542,920

Abbreviations: lcl - lower confidence limit (95% confidence interval);
ucl - upper confidence limit (95% confidence limit)
† Where England represents 80% of UK

Appendix 7-7 Average yearly healthcare costs amongst patients with GI infection only and those with sequelae in England, 2000-2015

Appendix 7-7-1 *Campylobacter* patients with G.I infection and those with sequelae

		GI Infection only			GI Infection and sequelae			Impact of sequelae	
Category		**After**	**Before**	**Difference (A-B)**	**After**	**Before**	**Difference (A-B)**	**Before[1]**	**After[2]**
	Mean cost	£119.1	£132.1	-£12.9	£190.5	£174.0	£16.6	£41.9	£71.4
	Std. error	1.158	1.024		10.248	9.330			
	LCI	£116.86	£130.06	-£15.97	£170.35	£155.58	-£10.66	£25.69	£53.10
	UCI	£121.40	£134.07	-£9.91	£210.74	£192.35	£43.81	£58.11	£89.73
Consultations	*P*-Vaue			<0.001			0.2322	<0.001	<0.001
	Mean cost	£146.1	£130.8	£15.3	£268.3	£160.6	£107.6	£29.9	£122.2
	Std. error	2.320	1.996		27.617	16.744			
	LCI	£141.54	£126.86	£9.31	£213.85	£127.65	£44.16	-£1.68	£85.21
	UCI	£150.63	£134.68	£21.31	£322.69	£193.64	£171.10	£61.42	£159.17
Prescriptions	*P*-Vaue			<0.001		0.0009		0.064	<0.001
	Mean cost	£33.0	£31.3	£1.7	£58.1	£39.9	£18.2	£8.6	£25.1
	Std. error	0.391	0.363		3.917	3.457			
	LCI	£32.26	£30.61	£0.66	£50.37	£33.07	£7.94	£2.81	£18.86
	UCI	£33.79	£32.03	£2.75	£65.81	£46.70	£28.47	£14.32	£31.27
Tests	*P*-Vaue			0.001			<0.001	0.004	<0.001
	Mean cost	£16.9	£7.6	£9.3	£40.4	£21.8	£18.6	£14.2	£23.5
	Std. error	0.648	0.447		10.618	11.730			
	LCI	£15.61	£6.72	£7.74	£19.47	-£1.31	-£12.50	£6.64	£13.03
	UCI	£18.15	£8.47	£10.82	£61.31	£44.91	£49.69	£21.77	£34.00
Outpatients	*P*-Vaue			<0.001			0.241	<0.001	<0.001

		GI Infection only			GI Infection and sequelae			Impact of sequelae	
Category		**After**	**Before**	**Difference (A-B)**	**After**	**Before**	**Difference (A-B)**	**Before[1]**	**After[2]**
	Mean cost	£358.0	£345.2	£12.8	£653.0	£385.4	£267.6	£40.2	£295.0
	Std. error	7.813	7.358		92.572	60.022			
	LCI	£342.69	£330.80	-£8.25	£470.62	£267.14	£50.80	-£76.05	£170.50
	UCI	£373.32	£359.64	£33.82	£835.43	£503.68	£484.43	£156.43	£419.54
Admissions	*P*-Vaue			0.234			0.016	0.498	<0.001
	Mean cost	£4.8	£3.5	£1.3	£19.9	£4.8	£15.2	£1.3	£15.2
	Std. error	0.197	0.175		3.027	1.766			
	LCI	£4.40	£3.19	£0.74	£13.98	£1.30	£8.27	-£1.52	£11.97
	UCI	£5.18	£3.87	£1.78	£25.91	£8.26	£22.05	£4.03	£18.34
Colonoscopy	*P*-Vaue			<0.001			<0.001	0.375	<0.001
	Mean cost	£677.9	£650.5	£27.4	£1,230.3	£786.5	£443.8	£136.0	£552.4
	Std. error	9.844	9.030		115.807	75.880			
	LCI	£658.62	£632.80	£1.23	£1,002.08	£636.97	£171.70	-£6.74	£395.50
	UCI	£697.21	£668.20	£53.59	£1,458.45	£936.00	£715.86	£278.71	£709.21
Total costs	*P*-Vaue			0.040			0.001	0.062	<0.001

[1]Difference between GI with sequelae and GI only in the quarters before (GI with sequelae before – GI only before) [2] Difference between GI with sequelae and GI only in the quarters after (GI with sequelae after – GI only after)

Appendix 7-7-2 NTS patients with GI infection and those with sequelae

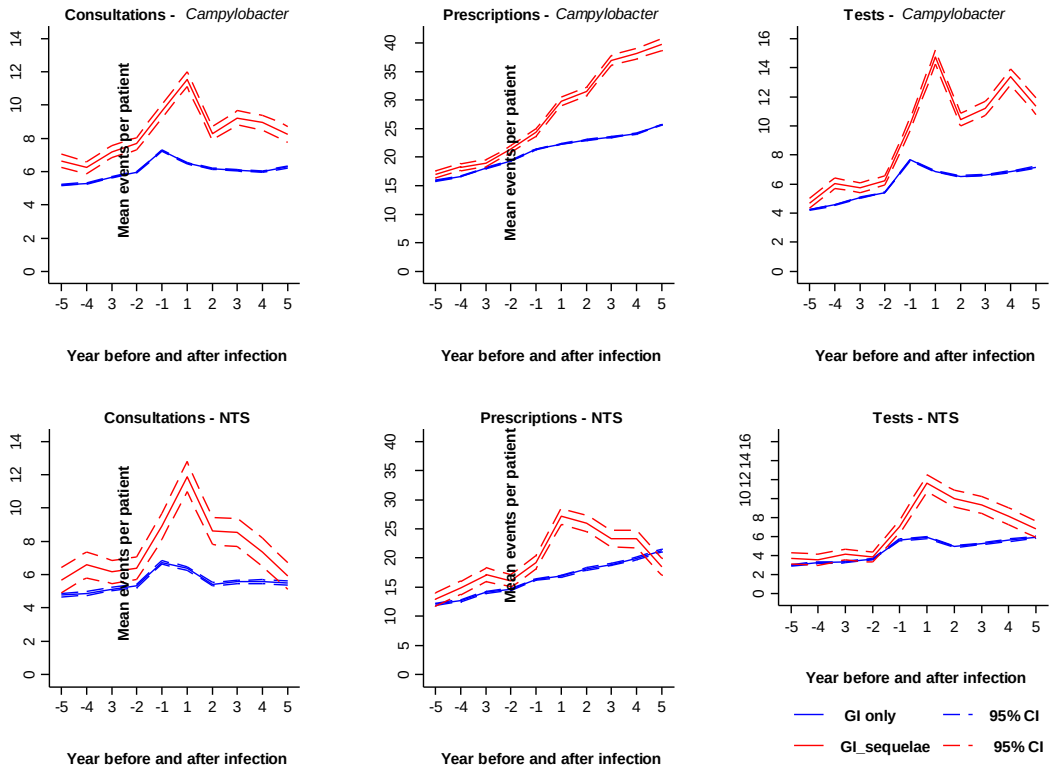
		GI Infection only			GI Infection and sequelae			Impact of sequelae	
Category		**After**	**Before**	**Difference (A-B)**	**After**	**Before**	**Difference (A-B)**	**Before[1]**	**After[2]**
	Mean cost	£113.3	£117.1	-£3.8	£179.3	£157.2	£22.1	£40.1	£66.0
	Std. error	2.682	2.359		17.713	19.088	26.040	£14.92	£16.85
	LCI	£108.03	£112.47	-£10.81	£143.80	£118.99	-£29.54	£10.87	£32.96
	UCI	£118.55	£121.72	£3.20	£214.77	£195.47	£73.65	£69.39	£99.03
Consultations	*P*-Vaue			0.2869			0.3987	0.007	<0.001
	Mean cost	£125.8	£99.3	£26.5	£186.5	£117.0	£69.5	£17.7	£60.7
	Std. error	6.025	4.263		32.288	19.815	37.883	£26.58	£37.66
	LCI	£113.99	£90.90	£12.08	£121.81	£77.27	-£5.53	-£34.43	-£13.17
	UCI	£137.62	£107.62	£41.02	£251.17	£156.65	£144.59	£69.82	£134.53
Prescriptions	*P*-Vaue			0.0003			0.0691	0.506	0.107
	Mean cost	£29.2	£23.4	£5.8	£57.1	£32.6	£24.5	£9.3	£28.0
	Std. error	0.907	0.801	1.210	9.535	6.696	11.651	£5.07	£5.82
	LCI	£27.39	£21.79	£3.43	£38.02	£19.22	£1.40	-£0.68	£16.54
	UCI	£30.94	£24.93	£8.18	£76.22	£46.05	£47.57	£19.22	£39.37
Tests	*P*-Vaue			0			0.0378	0.068	<0.001
	Mean cost	£9.9	£3.9	£6.0	£36.6	£11.2	£25.4	£7.3	£26.7
	Std. error	1.059	0.601		19.986	4.696	20.531	£3.79	£7.30
	LCI	£7.83	£2.75	£3.59	-£3.44	£1.82	-£15.30	-£0.14	£12.38
	UCI	£11.99	£5.11	£8.37	£76.64	£20.64	£66.05	£14.74	£41.01
Outpatients	*P*-Vaue			0			0.2191	0.055	<0.001
	Mean cost	£337.0	£355.7	-£18.7	£313.8	£212.5	£101.2	-£143.2	-£23.2
	Std. error	27.571	25.121		76.474	67.167	101.783	£155.90	£171.14
	LCI	£282.92	£306.43	-£91.82	£160.56	£77.98	-£100.45	-£448.89	-£358.85
	UCI	£391.06	£404.95	£54.43	£466.95	£347.08	£302.89	£162.57	£312.37
Admissions	*P*-Vaue			0.6162			0.3221	0.359	0.892

		GI Infection only			GI Infection and sequelae			Impact of sequelae	
Category		**After**	**Before**	**Difference (A-B)**	**After**	**Before**	**Difference (A-B)**	**Before[1]**	**After[2]**
	Mean cost	£4.1	£3.2	£0.9	£11.9	£2.1	£9.8	-£1.1	£7.8
	Std. error	0.477	0.484		4.252	2.106	4.745	£3.02	£3.03
	LCI	£3.17	£2.23	-£0.40	£3.35	-£2.11	£0.36	-£6.99	£1.81
	UCI	£5.04	£4.13	£2.26	£20.38	£6.32	£19.16	£4.84	£13.71
Colonoscopy	*P*-Vaue			0.1722			0.042	0.722	0.011
	Mean cost	£619.3	£602.5	£16.8	£785.1	£532.7	£252.4	-£69.8	£165.9
	Std. error	31.218	27.822		116.204	86.378	144.791	172.809	194.173
	LCI	£558.06	£547.96	-£65.22	£552.34	£359.65	-£34.45	-£408.71	-£214.93
	UCI	£680.49	£657.08	£98.74	£1,017.91	£705.72	£539.32	£269.05	£546.63
Total costs	*P*-Vaue			0.6557			0.084	0.686	0.393

[1]Difference between GI with sequelae and GI only in the quarters before (GI with sequelae before – GI only before) [2] Difference between GI with sequelae and GI only in the quarters after (GI with sequelae after – GI only after)

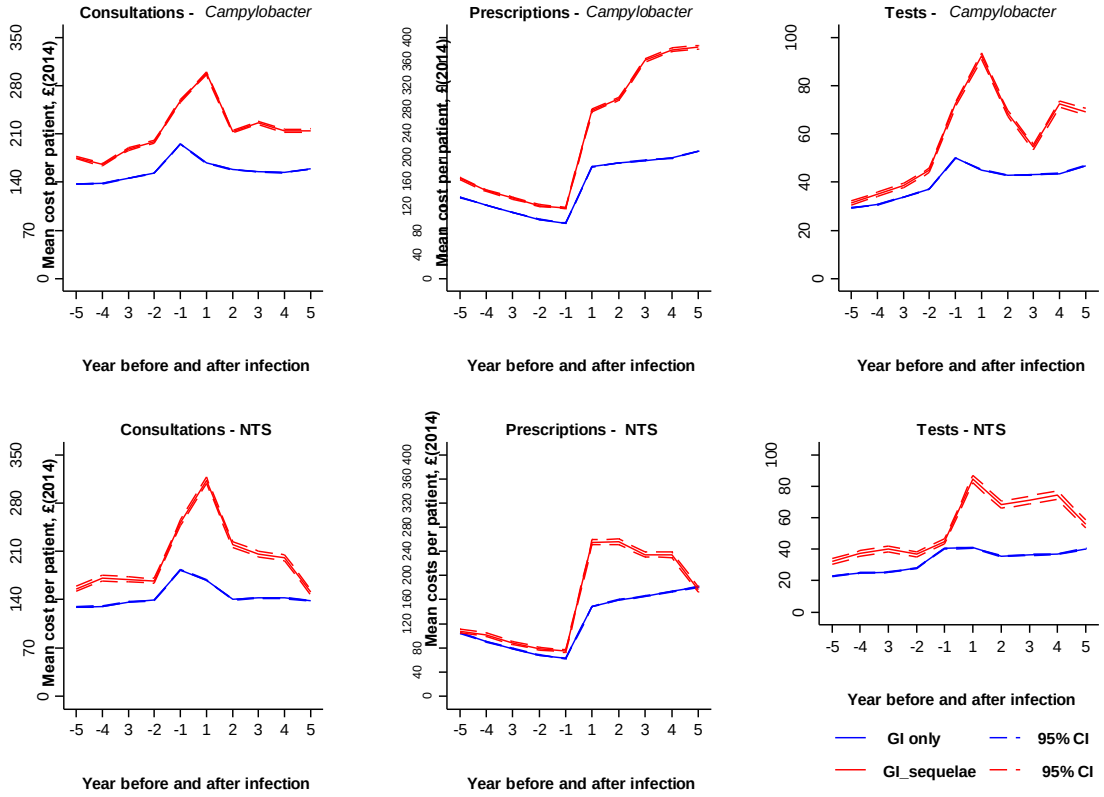
Appendix 7-8 Average yearly resource use amongst patients in the cohort

Appendix 7-8-1 Annual average number of primary care contacts per patient amongst patients with G.I only and those with sequelae up to 5 years before and after index date for infection



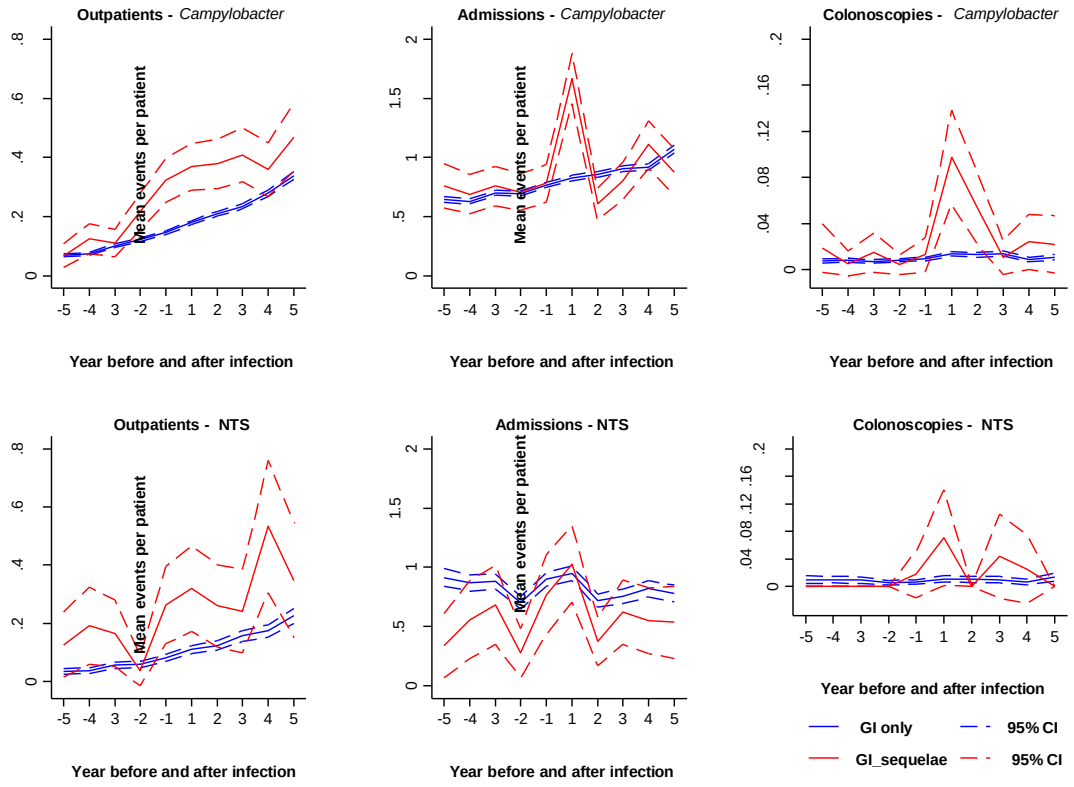
Appendix 7-7-1 shows the mean number of events per patient. Different scales used for each type of event

Appendix 7-8-2 Annual average cost of primary care contacts amongst patients with G.I only and those with sequelae up to 5 years before and after index date for infection



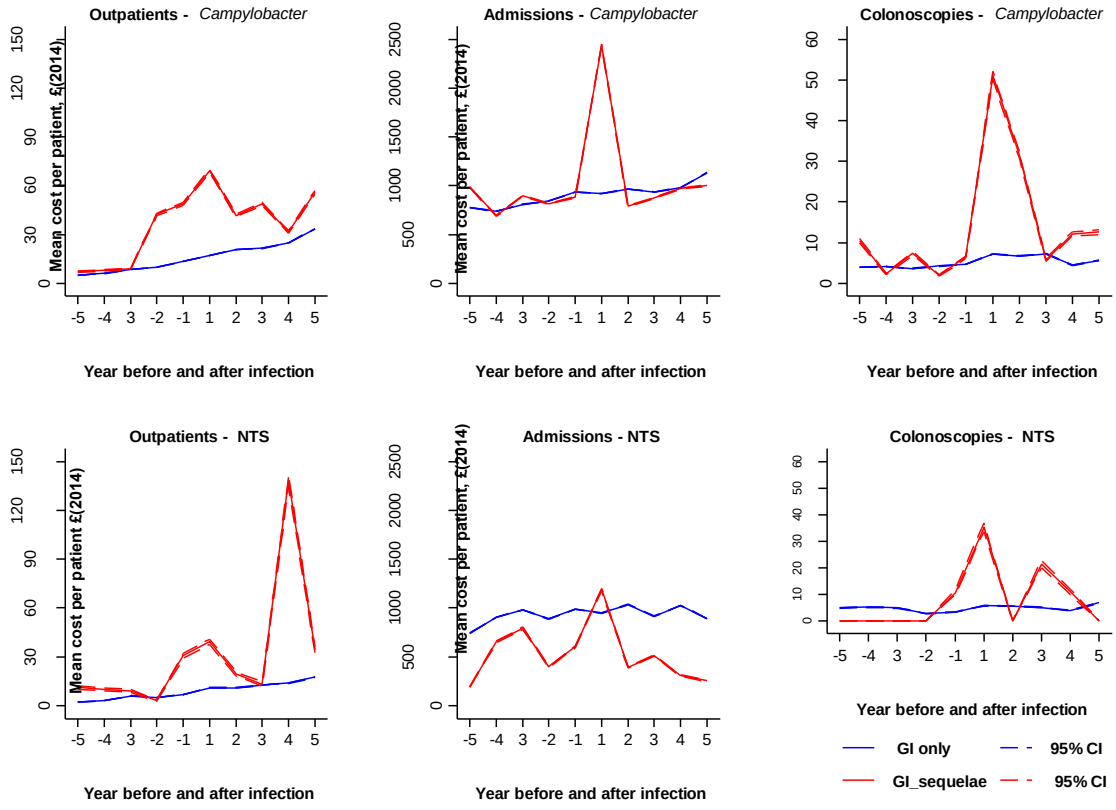
Appendix 7-7-2 shows the mean cost of events per patient. Different scales used for each type of event

Appendix 7-8-3 Annual average number of hospital contacts per patient amongst patients with G.I only and those with sequelae up to 5 years before and after index date for infection



Appendix 7-7-3 shows the mean number of events per patient. Different scales used for each type of event

Appendix 7-8-4 Annual mean number of hospital contacts per patient amongst patients with G.I only and those with sequelae up to 5 years before and after index date for infection



Appendix 7-7-4 shows the mean cost of events per patient. Different scales used for each type of event