Incidence, risk factors, and health service burden of sequelae of *Campylobacter* and Non-typhoidal *Salmonella* infections in England, 2000-2015: a retrospective cohort study using linked electronic health records

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ABSTRACT

Background Reactive arthritis, irritable bowel syndrome (IBS), Guillain-Barré syndrome, ulcerative colitis, and Crohn's disease may be sequelae of *Campylobacter* or non-typhoidal *Salmonella* (NTS) infections. Proton pump inhibitors (PPI) and antibiotics may increase the risk of gastrointestinal infections (GII); however, their impact on sequelae onset is unclear. We investigated the incidence of sequelae, their association with antibiotics and PPI prescription, and assessed the economic impact on the NHS.

Methods Data from the Clinical Practice Research Datalink for patients consulting their GP for *Campylobacter* or NTS infection, during 2000-2015, were linked to hospital, mortality, and Index of Multiple Deprivation data. We estimated the incidence of sequelae and deaths in the 12 months following GII. We conducted logistic regression modelling for the adjusted association with prescriptions. We compared differences in resource use and costs pre- and post-infection amongst patients with and without sequelae.

Findings Of 20,471 patients with GII (*Campylobacter* 17,838), less than 2% (347) developed sequelae, with IBS (268) most common. Among *Campylobacter* patients, those with prescriptions for PPI within 12 months before and cephalosporins within 7-days before/after infection had elevated risk of IBS (adjusted odds ratio [aOR] 2.1, 1.5-2.9) and (aOR 3.6, 1.1-11.7) respectively. *Campylobacter* sequelae lead to ~ £1.3 million, (£750,000, £1.7 million) in additional annual NHS expenditure.

Interpretation Sequelae of *Campylobacter* and NTS infections are rare but associated with increased NHS costs. Prior prescription of PPI may be a modifiable risk factor. Incidence of sequelae, healthcare resource use and costs are essential parameters for future burden of disease studies.

INTRODUCTION

Campylobacter spp. is the most common bacterial cause of gastrointestinal infection (GII) globally and in the United Kingdom (UK), while non-typhoidal Salmonella (NTS) is the leading cause of death amongst bacterial GII pathogens [1]. Despite several industry wide interventions and public health campaigns, *Campylobacter* incidence has remained relatively stable in the last decade and leads to 80,000 primary care consultations annually in the UK [2,3]. While NTS infections are on the decline but responsible for several multicountry outbreaks of recent [4,5]. Although these zoonotic infections are usually self-limiting intestinal complications of irritable bowel syndrome (IBS), Crohn's disease (CD) and ulcerative colitis (UC), and extra-intestinal manifestations such as reactive arthritis (ReA), Guillain-Barré Syndrome (GBS), and rheumatoid arthritis (RA) can occur [6].

Drugs which alter gastric pH, such as proton pump inhibitors (PPI) and antibiotics, can increase susceptibility to GII [7,8]. A Dutch case-control study reported that PPI usage was associated with repeated gastroenteritis episodes and risk of ReA following campylobacteriosis [9]. However, their overall role in post-infectious sequelae is uncertain.

These GII have high economic implications. According to 2008-09 UK data from the Intestinal Infectious Disease Study 2 (IID2), *Campylobacter* infections cost ~£50 million annually, 20% of which is due to direct healthcare costs, but GBS was the only sequela considered in this estimate [10]. Available cost estimates for NTS infections in the UK date back to the 1993-96 IID1 study with an overall cost of £46.4 million [11]. These estimates do not explore the influence of patients' characteristics in healthcare resource utilisation and associated costs. Exploiting patient-level heterogeneity can enable efficient allocation of healthcare resources, and provide targeted prevention strategies [12].

We aimed to determine the incidence of sequelae of *Campylobacter* and NTS infections; risk factors associated with sequelae onset; and the resulting impact on the volume, type, and costs of healthcare resources in primary and secondary settings in England.

Research in context

Evidence before this study

Campylobacter and non-typhoidal *Salmonella* (NTS) gastrointestinal infections (GI) are usually self-limiting illnesses, but sequelae including irritable bowel syndrome (IBS), reactive arthritis (ReA), Guillain Barré syndrome (GBS), ulcerative colitis (UC), Crohn's disease (CD) and rheumatoid arthritis (RA) increase the burden on patients and the health service. Which patient or pathogen factors increase the risk of these sequelae remains uncertain.

In a systematic review of studies reporting the onset of ReA (n =37), IBS (n =5) and GBS (n =9) published by our group in 2016, the incidence of sequelae varied depending on the study size and data source. Studies comprising large cohorts of > 10,000 reported a low incidence of ReA and IBS (< 1%), contrasting with outbreak investigation reports (up to 60%). Scarce (1 study) or weak evidence (6) was found of a relation between sequelae and PPI or antibiotics use, respectively.

We searched MEDLINE, Embase, and Web of Science from the date of the last search of the 2016 review (April 27, 2016) up to August 2019, for observational cohort studies and systematic reviews and meta-analyses reporting on associations of patient-related and pathogen-related factors in the onset of sequelae following GII. We used search terms related to the exposures "Campylobacter Infections", "Salmonella Infections", campylobacter*, salmonella* combined with those related to sequelae "Guillain-Barré Syndrome", "Inflammatory Bowel Diseases", "Irritable Bowel Syndrome", "Arthritis, Reactive", crohn*, colitis*, and "IBS". Our search was not restricted by language. We identified one registry study, which demonstrated increased risk of IBD following bacterial infection (adjusted odds ratio [aOR]1.6, 95% C.I 1.6-1.7) with risk elevated for antimicrobial treatment (aOR 4.2, 95% C.I 3.3-5.3), although pathogen-specific risk factor estimates were limited. The most recent systematic review of post-infectious IBS (PI-IBS) identified a study with elevated risk following antibiotic treatment in children only, while a previous review reported an association with antibiotics regardless of the population structure. Both reviews agreed on other factors associated with elevated risk of PI-IBS which include, individuals who were young, female, had a history of anxiety, depression and somatisation. However, one review included studies on both prevalence and incidence while the latter only focused on prevalence. Moreover, pathogen-specific risk factor estimates were lacking. Existing evidence for the role of patient-related factors on risk of post-infectious sequelae is limited by inadequate sample sizes, inconsistent follow-up durations, and substantial inter-study heterogeneity.

Added value of this study

Using a single large observational cohort of 20,471 patients with *Campylobacter* (17,838) or NTS (2,633) infections, this study estimated the pathogen-specific incidence of sequelae in England, associated risk factors, and the resulting economic burden on the NHS. Within 12 months post-infection, < 2% developed sequelae, with IBS most frequently diagnosed (1.1%). Female sex, age <65 years, previous long-term exposure to PPI, use of cephalosporins were associated with elevated risk of IBS. Sequelae of *Campylobacter* led to ~£1.3 million (95% C.I £750,000, £1.7 million) in additional NHS expenditure annually, while for NTS it was lower at ~£224,000 (95% C.I £0, £465,000). Males aged > 65 with pre-existing comorbidities accrued the highest costs.

Implications of all the available evidence

Despite several industry wide interventions and public health campaigns, *Campylobacter* incidence has remained stable, although NTS incidence is declining. These infections still pose a considerable burden on healthcare resources. Estimates of the clinical and economic consequences of sequelae are crucial in understanding the burden of these infections and can be incorporated into economic evaluation models to inform strategies for reducing the burden of these infections.

METHODS

Study design and population

In this cohort study, we identified patients with a recorded diagnosis of *Campylobacter* or NTS infection in the Clinical Practice Research Datalink (CPRD) between 2000-2015 during consultation with their General Practitioner (GP) (Appendix Table S1, p2). We followed up individuals from consultation date to the earliest of date of death, transfer out of GP practice or end of 2015. All patients were registered with their GP practice for at least 12 months before study entry for adequate measurement of baseline characteristics. Primary care data were linked to patients' hospital encounters (Hospital Episode Statistics – HES), mortality records (Office of National Statistics – ONS) and socioeconomic status (Index of Multiple Deprivation 2010 – IMD-2010). Datasets were linked by a trusted third party, NHS Digital for the Medicines and Healthcare products Regulatory Agency (MHRA) using the patient's NHS identification number, sex, date of birth, and postcode [13].

CPRD contains anonymised longitudinal data of all primary care encounters for over 14 million patients from general practices in the UK [14]. HES contains hospital encounters in England including information on deaths in the hospital from 1997 [15]. ONS death registration data contain the date and coded cause of death for England and Wales from 1998 [12] . HES and ONS data are coded using the International Classification of Diseases (ICD) versions 9 (2000 for ONS only) and 10 (all HES and 2001 onwards for ONS). The study was approved by the MHRA Independent Scientific Advisory Committee (16_112).

Procedures

For each patient, an index date was defined as the date of consultation for diagnosis of either *Campylobacter* or NTS. Only the first record was retained for recurrent episodes occurring within a month of the first episode. Patients with multiple infections recorded on the same date and those with a previous history of the conditions of interest were excluded. We extracted data on age, sex, socio-economic status (SES) quintile, smoking status and Charlson Comorbidity Index (CCI).

We considered the number of prescriptions for quinolones, macrolides and cephalosporins within 7-days before and after the index date. The period before diagnosis was included as clinicians may prescribe broad-spectrum antibiotics before the aetiology is confirmed. For PPI,

all prescriptions up to 12 months before the index date for adults (age 18+) were used, as in adults most adverse events associated with PPI are linked to long-term usage [16].

Outcomes

The primary outcomes were incidence of ReA and IBS within 12 months post-infection (PI). Secondary outcomes were the incidence of CD, UC, RA and GBS and deaths where infection or sequelae is listed as a cause of death. Sequelae were identified using Read codes in CPRD and ICD-10 codes in HES (Appendix Table S2, p2). Deaths within 12 months post-infection where any cause of death was *Campylobacter*, NTS, ReA, IBS, CD, UC, GBS and RA were also considered.

All health service utilisation for primary (consultations, tests, and prescriptions) (Appendix Tables S3 – S4, p3-22) and secondary healthcare (hospital admissions, outpatients and colonoscopies) in the five years before and after the index date were categorised to enable attachment of unit costs.

Statistical Analyses

Statistical analyses were performed in STATA version 14 (Stata Corporation, College Station, Texas, USA). Differences in the distribution of exposures, covariates and outcomes were examined using t-tests and chi-squared tests, with 95% confidence intervals (CI) unless otherwise stated.

Incidence of sequelae

In patients with *Campylobacter* or NTS, we estimated the incidence of sequelae, expressed as a percentage and as a rate per 1,000 person-years (py) of follow-up, for up to 1, 3, 6 and 12 months PI.

Risk factors associated with sequelae onset

We performed logistic regression to assess the effect of antibiotics and PPI on the risk of sequelae onset following confirmed infection with *Campylobacter* (there was insufficient power for NTS). Antibiotic and PPI prescriptions were initially treated as binary. Three multivariate model specifications were performed. Model 1 was used to adjust for age (continuous), sex, smoking status (none, former or current), and CCI (0 vs 1+). Model 2 included age as categorical (18-24, 25-44, 45-64, 65+) to determine linearity in the effect of

age. Model 3 included a categorisation of the total number of PPI prescriptions (no PPI prescriptions; up to 5; 6-10; 10+) to assess a dose-response relationship. Interactions between predictors (PPI, age, sex, smoking status, and comorbidity) were also assessed. Counts less than five were not reported, to prevent deductive disclosure.

Health service utilisation and costs

We assessed the impact of the diagnosis of infection and sequelae on the average resource use and costs incurred by each patient. Using the cohort with a linked record in HES, we considered all available data in the five years before and after the index date. Consultations, tests, prescriptions, hospital admissions and outpatient visits/procedures were reported as the average number of events per patient per quarter. We reported mean differences in observed resource use and costs between the periods before and after the index date alongside 95% CIs. Total costs per patient per quarter were further stratified by sex, age, presence or absence of comorbidities and SES. Mean estimates were compared using Student's t-test. Quarterly costs per patient were further extrapolated to determine the expected overall costs to the NHS, with error propagation to account for uncertainty in the final estimates [17] (Appendix Box 1, p23).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

Study population

Overall, 21,837 CPRD patients met the case definition for *Campylobacter* (18,964) or NTS (2,873), with linkage to HES/ONS/IMD-2010 available for 17,108 (78%) (Figure 1). Characteristics of patients without a linked record did not differ from those with linkage (Appendix Table S5). The onset of sequelae was determined amongst 20,471 patients (*Campylobacter* 17,838; NTS 2,633) after excluding patients with a previous history of the conditions of interest 1,276 (6.2%) (Figure 1).

Incidence of sequelae

Table 1 shows the characteristics of patients with GII only (i.e. without sequelae) and those who developed sequelae. The incidence of sequelae within 12 months PI was lower in *Campylobacter* patients, 1.5%, (274/17,838; 95%CI (1.4-1.7), than in NTS patients, 2.8%, (73/2,633); 95%CI (2.1-3.4). IBS was the most frequently recorded sequela (*Campylobacte*r patients, 74%, 203/274; NTS patients, 70%, 51/73), while ReA was higher amongst NTS patients (14%, 10/71) than *Campylobacter* patients (5%, 14/274). Sequelae patients were disproportionately likely to be females.

The incidence of *Campylobacter*-associated ReA was highest in the 1-month PI with a rapid decline subsequently (Figure 2). The rate of onset of *Campylobacter*-associated IBS remained stable (12.2 per 1,000 py, 95%CI(10.6-13.9) at up to 12 months PI) and was lower than NTS-associated IBS. The rate of NTS-associated IBS within 3 months was approximately double that for *Campylobacter* (30.0 per 1,000 py, 95%CI (19.4-46.5) vs 14.6 per 1,000 py, 95%CI (11.4-18.6)).

Deaths associated with sequelae

Fewer than five deaths were recorded in the 12 months PI; hence no further analysis was conducted to prevent deductive disclosure.

Risk factors associated with sequelae onset

Campylobacter patients with sequelae who had a prescription for antibiotics within seven days of the index date (38.4%, 105/274), mostly (68.6%, 72/105) had a prescription recorded on the same day as their consultation for GII (Table 1). Macrolides were the most frequently recorded

(64.8%, 68/105) while only cephalosporins was associated with an elevated risk of IBS (adjusted odds ratio [aOR] 3.6, 95%CI (1.1 – 11.7), *P*=0.033) using the predefined covariates (age, sex, CCI and smoking status (Figure 3).

Amongst *Campylobacter* patients aged 18 and over with sequelae, 26% (4,116/15,806) had a PPI prescription (Table 1). PPI prescription was associated with an elevated risk in the onset of IBS (aOR 2.1, 95%CI 1.5-2.9, *P*<0.001) (Figure 4). No effect was observed for the secondary outcomes. Female sex influenced the elevated risk of IBS in the multivariate analysis, while an increase in age had a protective effect with a significant trend across all the age groups (Model 1 and 2, Table 2, Appendix Figure S1).

When the total number of PPI prescriptions was used in place of the presence or absence of PPI as the independent variable, there was no significant trend in the risk of IBS with increased PPI prescription within the year preceding infection (Model 3, Table 2). There was also no evidence of any interaction with any of the covariates (Table 3).

Health service utilisation and costs

Sequelae of *Campylobacter* and NTS infections resulted in increased health service utilisation PI across all healthcare domains except for outpatients and hospital admissions in comparison with patients with GII only. This costs an average of £331.0, (95%CI (£260.7, £401.4) and £211.0, (95%CI £58.8, £364.3) per patient per quarter amongst *Campylobacter* and NTS patients respectively (Table 4). Consequently, the additional annual costs of sequelae of *Campylobacter* to the NHS was approximately £1.3 million (95% C.I £750,000, £1.7 million) for all patients who consulted their GP for their infection in England. Correspondingly, for NTS infections, a total cost of ~£224,000 (95% C.I £0, £465,000) annually was incurred (Appendix Table S6).

The difference in difference of the mean total costs in the periods' pre-and post-infection was higher for males with sequelae (£510.2, 95%CI (£413.0, £607.3)) than for females (£183.9, 95%CI (£98.1, £269.7)). Although the overall costs of sequelae were higher amongst patients aged 65 years and above (£603.5, 95%CI(£130.6, £859.4)) in comparison with younger age groups, there was a wide variation in the costs accrued by these patients due to the small sample size of this group.

Patients without sequelae living in the most affluent areas (IMD-1) accrued lower total costs PI than those living in the most deprived areas (IMD-5) (Table 5). For patients who developed sequelae, there was no clear distinction in costs accrued in the quarters PI stratified by IMD. The presence of comorbidity increased costs PI in comparison with patients with GII only (DID £566.2, 95%CI (£418.6, £713.9), P <0.001) (Table 4).

DISCUSSION

In this retrospective study of patients with *Campylobacter* or NTS infection, we found that the incidence of sequelae following these GII was low (1.7%), with IBS as the most frequently diagnosed. Female *Campylobacter* patients under 65 years of age with a prescription for PPI up to a year preceding infection were more likely to develop IBS. Those with a cephalosporin prescription in the seven days before/after infection also had a moderate elevated risk for the onset of IBS. Although the incidence of sequelae was low, the impact on the NHS was significant. Overall, the sequelae of *Campylobacter* infection led to an estimated £1.3 million in additional annual NHS healthcare expenditure in England, while sequelae of NTS infection produced a lower but substantial total cost of ~£224,000 (95% C.I £0, £460,000) annually.

The proportion of patients with a recorded diagnosis for IBS following *Campylobacter* (1.1%) or NTS (1.9%) in our study was higher than published estimates by Ternhag and colleagues using historical medical records (*Campylobacter*, 0.03-0.89 %; NTS, 0.01-1%) [18]. Our study incorporated outcomes from both primary and secondary care, while the earlier study only used hospital discharge records to determine sequelae. Thus, conditions commonly diagnosed in primary care settings, such as IBS, may have been underreported previously. In keeping with similar studies assessing the incidence of IBS within 12 months of *Campylobacter* infection, the rate of IBS following *Campylobacter* infection was ~ 6-fold higher than the reported incidence of IBS in the absence of GII (~ two per 1,000 person-years) [19]. The incidence of the secondary outcomes was low. Similar to other studies, we did not find evidence of GBS following NTS infection [6].

The elevated risk of IBS following PPI prescription was mainly driven by females of a younger age in the cohort (< 65 years old). The elevated risk reflects their overall increased propensity for the development of IBS symptoms regardless of a PPI prescription as there was no evidence of interactions. Many functional disorders in females may be attributed to gender-specific

factors such as circulating sex hormones and changes in rectal sensitivity during menstrual cycles. Increased prevalence of psychological symptoms of anxiety, depression and somatisation in females may also be modifiable factors associated with IBS [20]. Infection may trigger initial symptoms, while cognition, behaviour and emotions may prolong and maintain them over time [4].

Only prescriptions for cephalosporin was associated with the onset of IBS in our study. A systematic review assessing the factors associated with the prevalence of PI-IBS also reported an elevated risk following treatment with antibiotics but did not specify the class of antibiotics, age group or the pathogen-specific risk estimates; while another only identified a study with increased risk in children only [20,21]. Current guidelines recommend clarithromycin, a macrolide for *Campylobacter* infection for returning travellers – the main indication for treatment, and not cephalosporin, a broad-spectrum antibiotic linked to increased risk of *Clostridium difficile* [22]. The observed association with antibiotics should be interpreted with caution as only a small number of patients were prescribed cephalosporins and the significant result may be have arisen due to multiciplicity of testing in the regression model.

We did not find an association between the onset of any of the secondary outcomes and the prescriptions considered and it was not possible to examine some of them (GBS and CD). This is in contrast to a recent case-control study which found an increased odds of inflammatory bowel disease (aOR 1.6, 95% C.I 1.6-1.7) following antecedent GII with an elevated odds for antimicrobial treatment (aOR 4.16, 95% C.I 3.3-5.3), although treatment was rare amongst cases (1.5%) and CD or UC were not considered separately [21].

Stratification of resource use and costs by patient age, sex and CCI shows that patients aged 65 and over, males, and those with existing comorbidities who developed sequelae incurred the highest cost PI. Older age and living with comorbidities are common patient characteristics linked to increased healthcare utilisation and costs [23]. However, the patient groups which accrued the highest costs were not the same group of patients at risk of developing IBS following *Campylobacter* infection (younger females, <65). Consequently, the health service needs of patients at risk of sequelae may be masked by the healthcare usage of those with a propensity to access healthcare, such as older patients and those with existing comorbidities.

On average, approximately £330 extra in expenditure is incurred per quarter for every case of *Campylobacter* with sequelae. Published 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 total costs incurred [24–26]. The remaining 76-80% of total costs incurred were indirect non-healthcare related costs such as productivity losses.

Our study has several strengths. It uses patient-linked records across all the major healthcare access points in England. Database linkage allowed analysis of the temporal association between pathogen-specific diagnosis and sequelae onset and also limited the misclassification of prevalent cases as incident cases. The large size of the cohort increased the level of precision in estimating the incidence of rare outcomes and associated risk factors, with updated estimates on direct healthcare costs of sequelae.

Our estimates are generalisable to the population of England who consult for GII, as CPRD is a nationally representative data source. Community level estimates of sequelae of GII may be extrapolated with caution using ascertainment ratios from IID2 which measure the level of underreporting of IID amongst those who present to healthcare and the level in the community [2]. This is because 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. Confirmed cases of these GII may have a higher rate of sequelae than undiagnosed cases, leading to an overestimate of incidence of sequelae following these GII in the community.

Our study also has some limitations. Eligibility was based on Read codes following consultation for *Campylobacter* or NTS infections, which requires patients to have had a confirmed diagnosis from stool culture. Requests for stool culture may vary by GP, and when stool culture is requested, results may not be systematically recorded [27,28]. This may have introduced selection bias, as GPs are more likely to request a stool culture for patients who report foreign travel or have severe symptoms such as bloody or prolonged diarrhoea [27,28]. It was not possible to stratify patients by symptom severity, as this is usually recorded within a free-text field not available to researchers.

We did not include other possible indications for PPI prescription in the regression model. Only the CCI was used as a measure of pre-existing conditions, and this did not influence the risk

estimates. Further, we did not assess the length of PPI exposure and PPI dose. We did not include prescription of less potent acid-reducing drugs such as H2-receptor antagonist in the regression model following previous studies showing a stronger association with PPI and onset of adverse events [29].

The cost estimates in our study are from a payer's perspective and do not include direct estimation of costs borne by individuals, such as out-of-pocket expenses resulting from illness or societal costs from illness in patients and caregivers which include costs of lost productivity to patients/employers. This is beyond the scope of our study and presents an avenue for further research.

In summary, the incidence of sequelae of *Campylobacter* and NTS is low, but with a significant additional burden on healthcare resources, most notably amongst those who frequently access healthcare (older people and those with existing comorbidities). These heavy users were different from those at risk of sequelae such as IBS following *Campylobacter* infection who were females below the age of 65 years. The estimates from our study provide substantial baseline data in understanding the burden of these GII. These pathogen-specific estimates can be incorporated into the burden of disease studies to inform prevention strategies.

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Potential conflicts of interest

RP received funding from the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre, NIHR Oxford Medtech and In-Vitro Diagnostics Co-operative, NIHR Applied Research Collaboration Oxford and Thames Valley, and the Oxford Martin School during the conduct of the study.

Author contributions

OE, RP, NM, TF, and MV all designed the study and secured all ethical approvals. OE, TF and MV were responsible for data collection while OE completed all data analyses. OE, RP, NM, TF, and MV interpreted the results. OE drafted the manuscript. NM, TF, and MV made suggestions to manuscript drafts. TF and MV contributed equally.

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TABLES

Table 1 Characteristics of patients with *Campylobacter* and NTS infections with or without sequelae selected from CPRD with or without linkage to HES, 2000-2015

	Campylobacter			Non-typhoidal *Salmonella*		
	GII only, N=17,564	Sequelae, N = 274	*P-value*	GII only, N=2,560	Sequelae, N =73	*P*-value
Age (years), mean (Sd)	44.7 (21.2)	45.6 (17.2)	0.91	36.5 (23.3)	40.3 (17.2)	0.12
Age group (years)						
0-4	911 (5.2)	0 (0.0)	<0.001	288 (10.9)	†	0.002
5-14	819 (4.7)	7 (2.6)		359 (13.5)	5 (6.8)	
15-24	1,556 (8.9)	37 (13.5)		259 (9.8)	10 (13.7)	
25-44	5,031 (28.6)	89 (32.5)		684 (25.8)	22 (30.1)	
45-64	5,868 (33.4)	98 (35.8)		714 (26.9)	31 (42.5)	
65+	3,379 (19.2)	43 (15.7)		346 (13.1)	††	
Sex						
Male	9,455 (53.8)	99 (36.1)	<0.001	1307 (49.3)	28 (38.4)	0.06
Female	8,109 (46.2)	175 (63.9)		1343 (50.7)	45 (61.6)	
Index of multiple deprivation						
1	4,119 (23.5)	71 (25.9)	0.44	570 (21.5)	17 (23.3)	0.65
2	3,565 (20.3)	62 (22.6)		479 (18.7)	16 (21.9)	
3	2,710 (15.4)	35 (12.7)		423 (16.5)	13 (17.8)	
4	2,076 (11.8)	32 (11.7)		352 (13.8)	†	
5	1,268 (7.2)	15 (5.5)		233 (9.1)	†	
missing	3,826 (21.8)	59 (21.5)		503 (19.6)	16 (21.9)	
Smoking status						
Ever smoked	5,197 (29.6)	79(28.8)	0.18	712 (26.9)	19 (26.0)	0.66
Never smoked	11,152 (63.5)	167 (60.9)		1,787 (67.4)	48 (65.8)	
Missing	1,215 (6.9)	28 (10.2)		151 (5.7)	6 (8.2)	
Comorbidities						
None	174 (63.5)	11,526 (65.6)	0.46	1,928 (72.8)	51 (69.9)	0.58
1 or more	100 (36.5)	6,038 (34.4)		722 (27.2)	22 (30.1)	
Antibiotics						
Yes	6,395 (36.4)	105 (38.3)	0.52	737 (27.8)	24 (32.9)	0.34
Antibiotics Class						
Macrolides	3,726 (58.3)	68 (64.8)	0.078	50 (1.9)	1 (1.4)	0.61
Quinolones	2,606 (40.8)	34 (12.4)		672 (25.4)	23 (31.5)	
Cephalosporins	63 (1.0)	†		15 (0.6)	0 (0.0)	
*Antibiotics R_x Day**						
1-7 before	766 (12.0)	13 (4.7)	0.93	100 (3.8)	7 (9.6)	0.038
0	4,375 (68.4)	72 (68.6)		461 (17.4)	15 (20.5)	
1-7 after	1,256 (19.6)	20 (19.0)		176 (6.6)	†	
No	11,167 (63.6)	169 (61.7)		1,913 (72.2)	49 (67.1)	
PPI[‡]						
Yes	4,027 (25.9)	89 (33.5)	0.005	394 (20.3)	16 (24.6)	0.4
No	11,517 (74.1)	177 (66.5)		1,545 (79.7)	49 (75.4)	
Hospitalised						
No	17,027 (96.9)	266 (97.1)	0.9	2,514 (94.9)	68 (93.2)	0.51
Yes	537 (3.1)	8 (2.9)		136 (5.1)	5 (6.8)	
Sequelae						
ReA	-	14 (5.1)		-	10 (13.7)	
IBS	-	203 (74.1)		-	51 (69.9)	
UC	-	28 (10.2)		-	††	
CD	-	10 (3.6)		-	7 (9.6)	
RA	-	11 (4.0)		-	†	
GBS	-	8 (2.9)		-	0	

sd – Standard deviation; Hospitalised- Patients hospitalised within 30 days of GII in CPRD;† events less than 5 reduce deductive disclosure in accordance with the protocol; ††events suppressed to prevent deductive disclosure of figures in the table; *Antibiotics Rx Day – Day of prescription of antibiotics in the 7 days before or after consultation for GII, where 0 is the day of consultation; [‡]PPI only considered amongst patients aged 18 and over, n =15,806.

Table 2 Summary of logistic regression model to assess the relationship between prescription of PPI and the onset of IBS following *Campylobacter* infection

Patients included in each model, n = 15,806

Model	Factor	aOR‡ IBS[1]	[95% C.I]		*P*-value
Model 1	*PPI*	2.1	1.5	2.9	<0.001
	Age	0.97	0.96	0.98	<0.001
	Sex				
	Males	Referent			
	Females	2.5	1.9	3.4	<0.001
	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
	Comorbidity				
	None	Referent			
	1 or more	1.3	0.5	0.7	2.35
Model 2	*PPI*	2.1	1.5	2.9	<0.001
	Age				
	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				
	Males	Referent			
	Females	2.5	1.9	3.4	<0.001
	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
	Comorbidity				
	None	Referent			
	1 or more	0.9	0.7	1.3	0.716
Model 3	*Total PPI*				
	0	Referent			
	1-5	2.1	1.4	3	<0.001
	5-10	2	1.2	3.3	0.01
	>10	2.5	1.4	4.4	<0.001
	Age	0.97	0.96	0.98	<0.001
	Sex				
	Males	Referent			
	Females	2.5	1.9	3.4	<0.001
	Smoking status				
	Non-smokers/missing	Referent			
	Current	0.8	0.6	1.2	0.264
	Ex-smokers	1.1	0.7	1.9	0.660
	Comorbidity				
	None	Referent			
	1 or more	0.9	0.7	1.3	0.724

Abbreviations and symbols: ‡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;[2] - time of onset post-infection

Table 3. Interaction terms for multivariable logistic regression to assess relation between prescription of PPI and the onset of IBS following *Campylobacter* infection

Factor	OR‡	[95% C.I]		*P*-Value
PPI				
No	Referent			
Yes	2.9	0.9	8.7	0.063
Sex				
Male	Referent			
Female	2.5	1.2	5.6	0.02
Agegrp				
18-24	Referent			
25-44	0.7	0.3	1.6	0.424
45-64	0.4	0.2	0.9	0.02
65+	0.2	0.1	0.6	0.007
Smoking				
Missing/None	Referent			
Current	0.9	0.4	1.6	0.579
Ex-smokers	1.1	0.5	2.5	0.856
CCI				
None	Referent			
1 or more	0.9	0.6	1.3	0.448
Interactions				
PPI#Sex				
Yes#Female	1.1	0.5	2.3	0.768
PPI#Agegrp				
Yes#25-44	0.6	0.2	1.9	0.359
Yes#45-64	0.6	0.2	1.8	0.343
Yes#65+	0.9	0.2	3.2	0.822
Sex#Agegrp				
Female#25-44	0.7	0.3	1.7	0.443
Female#45-64	1.3	0.5	3.5	0.557
Female#65+	0.9	0.2	3.0	0.808
PPI#Smoking				
Yes#Current	1.3	0.4	1.8	0.64
Yes #Ex-smoker	0.8	0.3	5.4	0.644
PPI#CCI				
1 or more	1.3	0.7	2.5	0.441

Abbreviations and symbols: ‡Odds ratio; 95% Confidence Interval; *P*-value likelihood ratio test

Table 4a Average quarterly healthcare utilisation amongst patients with *Campylobacter* or NTS infection (with or without sequelae) in the quarters preceding and after infection in England, 2000-2015

	Resource use for patients with *Campylobacter* infection								
	GII only			**GII 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 (0.02)	2.1 (0.02)	-0.3 (-0.3 -0.2)*	3.3 (0.2)	2.8 (0.1)	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 (0.08)	5.4 (0.08)	-0.06 (-0.3, 0.2)	7.3 (0.6)	6.1 (0.5)	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 (0.02)	1.9 (0.02)	-0.3 (-0.4, -0.2)*	3.6 (0.3)	2.5 (0.2)	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 (0.002)	0.04 (0.002)	0.006 (0.001, 0.01)*	0.09 (0.02)	0.08 (0.02)	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	0.1 (0.002)	0.09 (0.003)	0.0003 (-0.007, 0.007)	0.3 (0.06)	0.10 (0.02)	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 (0.002)	0.002 (0.0002)	0.0009 (0.0003, 0.002)*	0.02 (0.005)	0.003 (0.002)	0.02 (0.01, 0.03)*	0.02 (0.02, 0.02)**	0.0009 (-0.002, 0.004)	0.02 (0.02, 0.03)**
	Resource use for patients with *NTS* infection								
Consultations	1.8 (0.04)	2.0 (0.04)	-0.2 (-0.3, -0.03)*	3.4 (0.4)	2.5 (0.2)	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 (0.2)	4 .1(0.2)	-0.1 (-0.6, 0.4)	6.7 (1.3)	4.8 (0.9)	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 (0.05)	1.4 (0.05)	-0.02 (-0.2, 0.1)	2.9 (0.5)	1.8 (0.3)	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 (0.005)	0.02 (0.003)	0.005 (-0.006, 0.02)	0.07 (0.03)	0.1 (0.03)	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 (0.02)	0.1 (0.02)	-0.1 (-0.06, 0.04)	0.2 (0.04)	0.1 (0.03)	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 (0.0006)	0.002 (0.0005)	0.001 (-0.0004, 0.002)	0.02 (0.009)	0.004 (0.004)	0.01 (-0.006, 0.03)	0.01 (0.008, 0.02)**	-0.003(-0.003, 0.009)	0.01 (0.003, 0.02)*

[1] Standard error in parentheses; [2] 95% Confidence interval in parentheses; After[3](mean quarterly utilisation rate in the periods after infection for patients with selected GII and sequelae – mean quarterly utilisation rate in the periods after infection for patients with GII only) Before[4]-(mean quarterly utilisation rate in the periods before infection for patients with GII and sequelae – -(mean quarterly utilisation rate in the periods before infection for patients with selected GII 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 <0.01

Table 4b Average quarterly healthcare costs amongst patients with *Campylobacter* or NTS infection (with or without sequelae) in the quarters preceding and after infection in England, 2000-2015

	Healthcare costs accrued by patients with *Campylobacter* infection								
	GII only			**GII 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	47.8(0.5)	56.4 (0.5)	-8.6 (-10.0, -7.3)*	85.4 (4.8)	74.5 (4.5)	-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 (0.7)	44.5(0.5)	-0.5 (-2.4, 1.4)	68.6 (5.7)	53.9 (5.1)	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 (0.2)	10.7 (0.17)	-1.8 (-2.3, -1.4)*	22.7 (2.2)	18.1 (1.6)	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 (0.3)	3.04 (0.20)	0.7 (0.1, 1.4)*	17.01 (8.4)	12.3 (6.6)	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 (3.5)	115.4 (3.4)	-9.7 (-19.3, -0.1)	380.5 (84.0)	114.7 (24.7)	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 (0.1)	1.2 (0.1)	0.5 (0.2, 0.8)*	12.6 (2.4)	1.6 (0.9)	11.0 (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 (4.0)**	**233.0 (2.8)**	**-19.4 (-30.4, -8.4)***	**586.7 (88.5)**	**75.1 (31.1)**	**311.6 (127.3, 495.9)***	**373.2 (304.5, 439.8)****	**42.1 (-20.0, 104.3)**	**331.0 (260.7, 401.4)****
	Healthcare costs accrued by patients with *NTS* infection								
Consultations	48.1 (1.2)	53.6 (1.1)	-5.5 (-8.7, -2.3)**	89.6 (9.2)	70.2 (7.6)	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 (1.5)	35.8 (1.5)	-0.5 (-4.8, 3.7)	63.0 (9.7)	42.3 (7.9)	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 (0.4)	10.1 (0.4)	-0.4 (-1.5, 0.6)	20.9 (4.0)	11.2 (2.1)	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 (1.0)	1.7 (0.2)	0.9 (-1.2, -3.0)	5.3 (2.2)	5.5 (2.5)	-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 (10.1)	122.9 (9.3)	-21.3 (-48.2, 5.7)	198.1 (56.9)	68.6 (25.2)	129.6 (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 (0.3)	0.8 (0.2)	0.5 (-0.2, 1.2)	8.7 (4.3)	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 (11.2)**	**224.9 (10.4)**	**-26.5 (-56.1, 3.6)**	**385.7 (69.9)**	**200.4 (35.0)**	**185.3 (30.4, 340.2)***	**187.1 (49.8, 324.4)***	**-24.5 (-150.7, 101.8)**	**211.5 (58.8, 364.3)***

All figures in £; [1] Standard error in parentheses; [2] 95% Confidence interval in parentheses; After[3](mean quarterly costs in the periods after infection for patients with GII and sequelae – mean quarterly costs in the periods after infection for patients with GII only) Before[4]-(mean quarterly costs in the periods before infection for patients with GII and sequelae – (mean quarterly costs in the periods before infection for patients with GII 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 <0.01

Table 5 Total costs per patient by sex, age group and deprivation quintiles for patients with *Campylobacter* and NTS GII with or without sequelae in England, 2000-2015

Patients with GII only (N= 16,822)				Patients with GII 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)	202.1 (192.4, 211.9)	253.3 (243.7, 263.0)	-51.2 (-64.9, -37.5)**	*n = 107*	710.4 (400.4, 1020.3)	238.4 (158.2, 318.6)	472.0 (153.6, 790.3)*	481.0(388.0, 573.9)**	-29.2 (-114.5, 56.1)	510.2 (413.0, 607.3)**
Females (n =8,067)	254.0 (242.5, 265.5)	301.9 (290.6, 313.2)	-47.9 (-64 - 31.8)**	*n =179*	497.2 (361.1, 633.3)	363.7 (295.9, 431.5)	133.5 (-18.0, 285.0)	235.4 (156.0, 314.8)**	51.5 (-23.3 126.3)	183.9 (98.1 269.7)**
0-17 yrs (n = 2,269)	99.6 (91.4, 107.9)	164.9 (150.8, 179.0)	-65.3 (-81.6, -49)**	*n = 15*	284.3 (114.8, 453.8)	156.4 (92.9, 220.0)	127.9 (-45, 300.7)	146.3 (49.1, 243.4)*	-43.9 (-214.6, 126.7)	190.2 (22.5, 357.9)*
18-44 yrs (n = 6,186)	151.8 (141.9, 161.6)	198.0 (188.3, 207.8)	-46.3 (-60.1, -32.4)**	*n = 128*	323.9 (244.7, 403.0)	216.9 (166.3, 267.6)	106.9 (13.4, 200.4)*	159.1 (89.6, 228.6)**	14.8 (-52, 81.6)	144.3 (71.5, 217.1)**
45-64 yrs (n = 4,999)	226.8 (214.2, 239.4)	271.5 (259.7, 283.3)	-44.7 (-62, -27.4)**	*n = 96*	669.4 (338.5, 1,000.2)	295.7 (228, 363.5)	373.6 (38.1, 709.2)*	421.6 (321.1, 522.2)**	7 (-76.5, 90.5)	414.7 (307.4, 521.9)**
65 yrs + (n = 3,093)	477.2 (450.6, 503.8)	529.3 (503.9, 554.8)	-52.1 (-89, -15.3)**	*n= 43*	1,248.6 (726.9, 1,770.3)	705.9 (459.3, 952.4)	542.7 (-25.9, 1,111.3)	768.8 (537.5, 1,000)**	165.4 (-47.7, 378.6)	603.4 (347.4, 859.4)**
IMD - Q1 (n = 4,973)	199.7 (187.5, 211.8)	239.1 (227.4, 250.9)	-39.5 (-56.4, -22.6)**	*n = 91*	369.2 (206.0, 532.4)	295.2 (199.4, 391)	74 (-114, 262)	165.9 (75.3, 256.5)**	45.9 (-39.5, 131.3)	120.0 (19.7, 220.3)*
IMD - Q2 (n = 4,335)	217.5 (203.6, 231.4)	266 (252.1, 279.9)	-48.4 (-68.1, -28.8)**	*n = 84*	780.7 (398.6, 1,162.9)	390.7 (268.8, 512.5)	390.1 (-8.1, 788.3)	541.1 (429.9, 652.4)**	97.5 (-1.4, 196.3)	443.7 (327.2, 560.2)**
IMD - Q3 (n = 3,335)	240.9 (222.5, 259.3)	300.3 (281.5, 319.0)	-59.3 (-85.6, -33.1)**	*n= 49*	458.1 (297.3, 618.9)	212.4 (147.9, 276.9)	245.7 (74.7, 416.8)*	189.0 (37.3, 340.7)*	-77.6 (-228.6, 73.4)	266.6 (107, 426.3)*
IMD - Q4 (n = 2,585)	233 (215.4, 250.5)	285.1 (268.2, 302.1)	-£52.2 (-76.5, -27.8)**	*n= 41*	676.9 (409.4, 944.5)	347.5 (213.8, 481.2)	329.5 (35, 624)*	420.1 (277.5, 562.7)**	74 (-58.1, 206.2)	346.1 (193.7, 498.4)**

Patients with GII only (N= 16,822)				Patients with GII 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]**
IMD - Q5 (n = 1,582)	299.2 (266, 332.3)	359.1 (327.3, 390.9)	-59.9 (-105.8, -14.0)**	*n = 20*	776.6 (-93.9, 1647.1)	295.8 (172.5, 419)	480.9 (-369.5, 1331.2)	495.2 (185.7, 804.7)*	-118.8 (-395.8, 158.2)	614.0 (287.6, 940.3)**
CCI - no (n= 11,150)	136.5 (129.8, 143.2)	148.1 (142.3, 153.9)	-11.6 (-20.5, -2.7)*	*n=183*	297.6 (215.4, 379.8)	147.6 (118.8, 176.3)	150.0 (63.2, 236.9)**	161.1 (107.7, 214.5)**	-0.5 (-46.2, 45.1)	161.6 (104.2, 219)**
CCI - yes (n=5,672)	359.3 (342.3, 376.3)	396.8 (379.5, 414.0)	-37.5 (-61.7, -13.2)*	*n= 103*	989.2 (634, 1344.3)	460.4 (336.1, 584.7)	528.8 (154.7, 902.8)**	629.9 (495.2, 764.5)**	63.6 (-65.7, 192.9)	566.2 (418.6, 713.9)**

All figures in £; *P <0.05; **P<0.001; After[1] – (Mean cost quarters after infection for patients with GII and sequelae – Mean cost quarters after infection for patients with GII only) Before[2]-(Mean cost quarters before infection for patients with GII and sequelae – Mean cost quarters before infection for patients with GII only); DID[3] – Difference in mean differences (After[1] - Before[2]); IMD – Index of Multiple Deprivation; Q – Quintile, Q1 – Least deprived, Q5 – Most deprived; CCI – Charlson comorbidity index

FIGURES

Figure 1 Study population

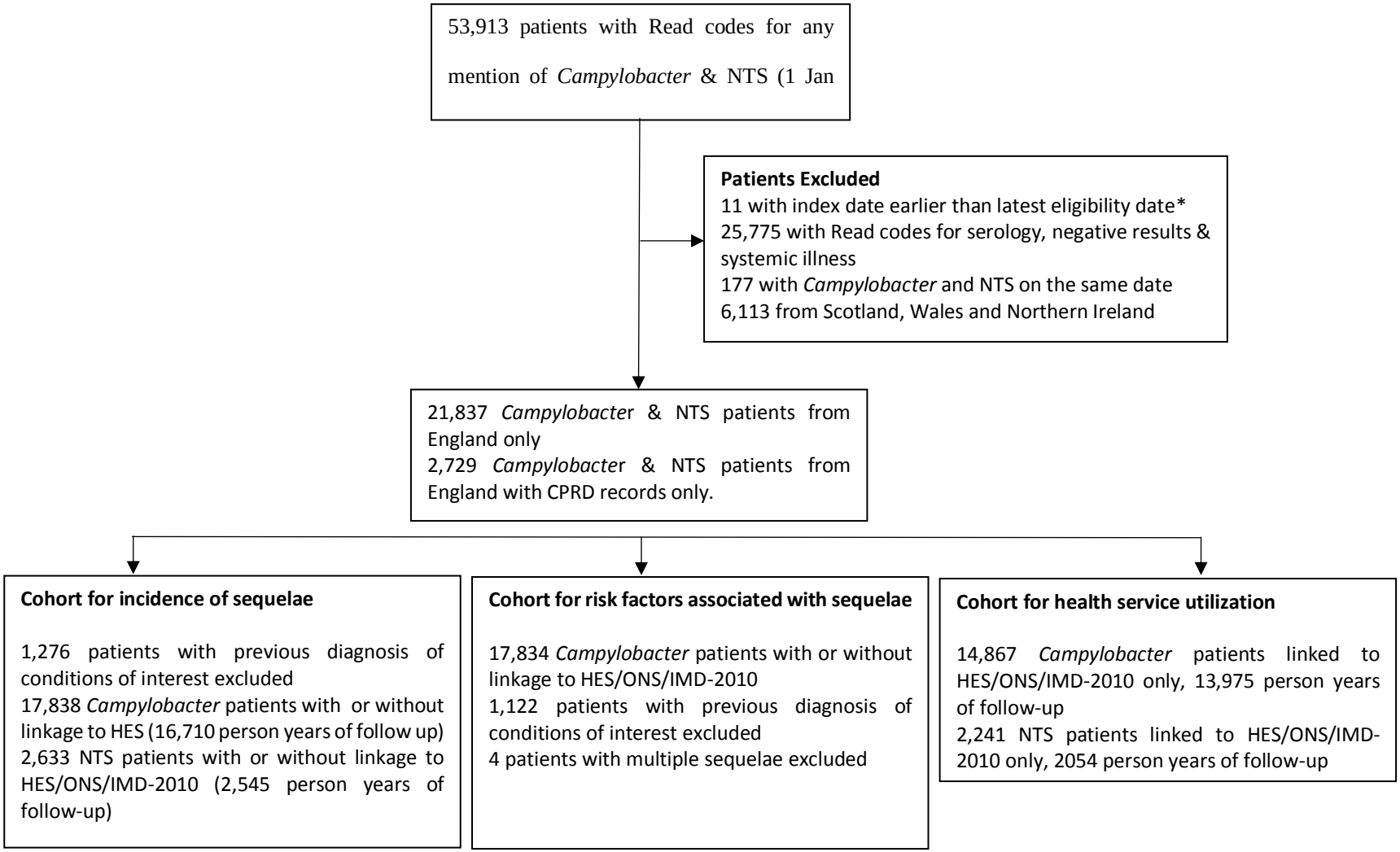
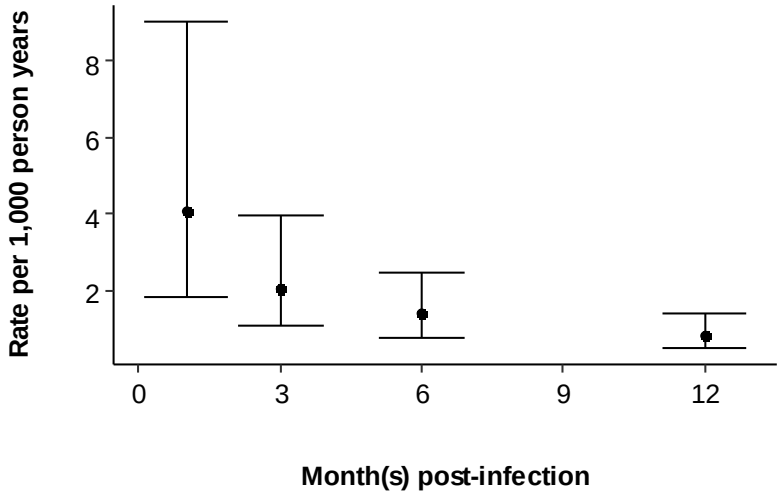
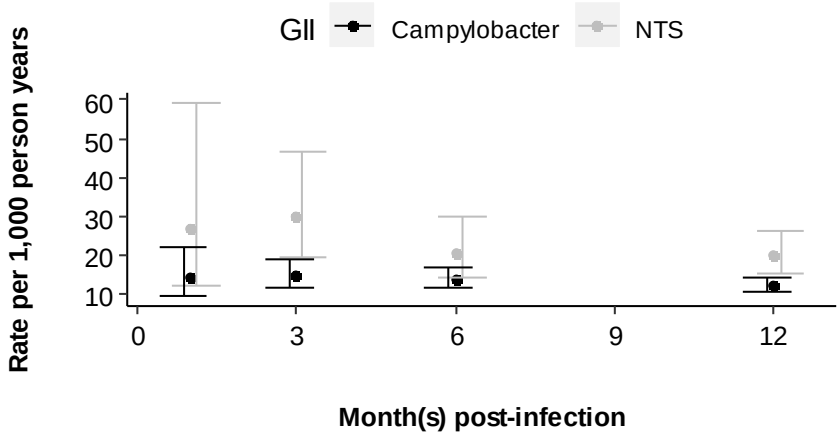


Figure 2a Rate of onset of reactive arthritis following *Campylobacter* infection in England, 2000-2015



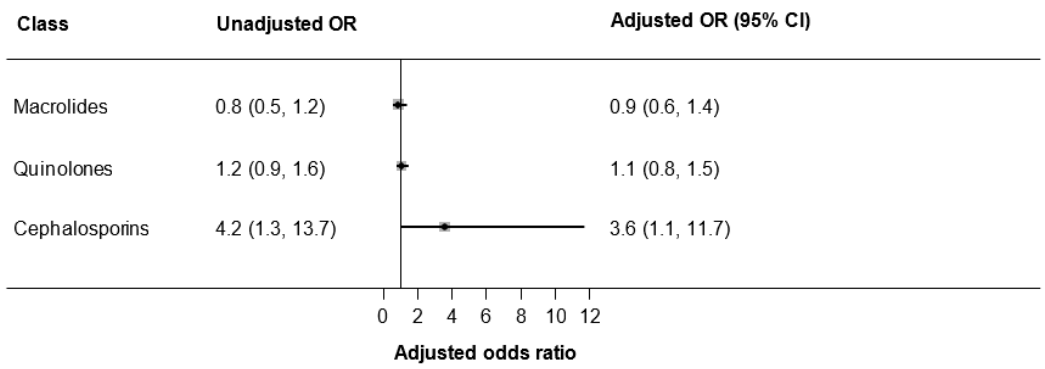
Error bars represent 95% confidence intervals. Deductive disclosure at 1-month post-infection for NTS associated ReA prevented fitting a plot.

Figure 2b Rate of onset of irritable bowel syndrome following *Campylobacter* or NTS infection in England, 2000-2015



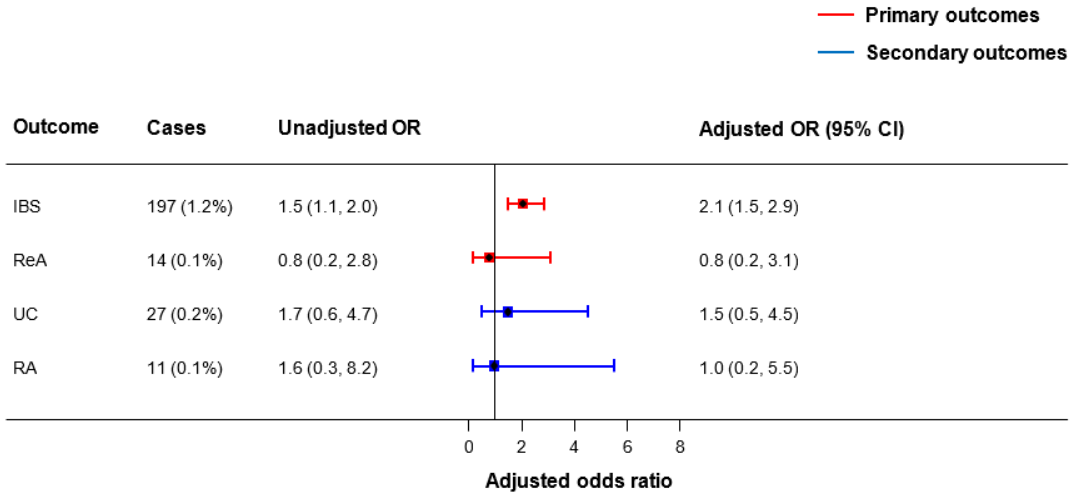
Error bars represent 95% confidence intervals

Figure 3. Association between class of antibiotics prescribed and the onset of irritable bowel syndrome amongst *Campylobacter* patients



Adjusted odds ratio (adjusted for age, sex, smoking status and Charlson comorbidity index)

Figure 4. Association between proton pump inhibitors and the onset of sequelae amongst *Campylobacter* patients



Adjusted odds ratio (adjusted for age, sex, smoking status and Charlson comorbidity index); IBS -irritable bowel syndrome; ReA -reactive arthritis; UC – ulcerative colitis; RA – rheumatoid arthrithis; small numbers precluded testing for any association between PPI and the onset of Crohn's disease

Figure Legends

Figure 1

Figure 1 shows the study population for the three main objectives based on the selection criteria.

Figure 2a

Figure 2a shows the incidence of reactive arthritis following *Campylobacter* infection up to 12 months post-infection.

Figure 2b

Figure 2b shows the incidence of irritable bowel syndrome following *Campylobacter* and NTS infection up to 12 months post-infection.

Figure 3

Figure 3 shows the logistic regression model for the association of three classes of antibiotics (macrolides, quinolones and cephalosporins) and the onset of irritable bowel syndrome up to 12 months following *Campylobacter* infection.

Figure 4

Figure 4 shows the logistic regression model for the association of prescription of proton pump inhibitors within 12 months before *Campylobacter* infection and the onset of reactive arthritis, irritable bowel syndrome, ulcerative colitis and rheumatoid arthritis following *Campylobacter* infection.