Evaluating effects of antibiotic treatment on resistance and patient outcomes using linked microbiology and patient electronic health record data

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ABSTRACT

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There is substantial pressure on medical services to reduce antibiotic prescribing, aimed at reducing the spread of antimicrobial resistance. Reducing prescribing in the acute hospital setting provides unique challenges, with antibiotic decisions made in the first few hours of admission with uncertainty over both diagnosis and severity of illness. The potential benefit to the patient must be balanced with the risks of side-effects and of future resistant infections to both the patient and the population as a whole.

I first review the evidence currently available to the acute clinician to assist in this decision. I then conduct a small study of antibiotic use in the acute medical setting, demonstrating that whilst substantially reducing antibiotic initiation and prescribing is possible, this is at the cost of more admissions and longer length-of-stay. I highlight the need for larger studies to meaningfully assess clinical outcomes, including resistant infections.

I then perform two studies investigating the accuracy of electronic health record data. The first assesses to what degree diagnostic codes can be used to estimate Charlson comorbidities to enable risk-adjusted studies of clinical outcome, concluding that diagnostic coding is relatively robust. The second assesses the degree to which diagnostic codes can be used to identify infections and their bacterial cause, finding that careful data curation is required, and significant limitations exist in using coded data to study causative organisms.

I use results from these studies to inform the subsequent design of a study of patients with *Escherichia coli* and *Klebsiella pneumoniae* bloodstream infections using linked electronic health record data and laboratory microbiology results. I find that previous broad-spectrum beta-lactams and trimethoprim exposure are associated with beta-lactam resistance in these infections at the level of an individual patient, but no evidence of association between duration of antibiotic exposure and development of resistance.

This work supports current efforts to limit use of broad-spectrum antibiotics, particularly beta-lactams, and to encourage the clinician, if an antibiotic is required, to try and use narrow spectrum antibiotics. It also showcases the power of electronic health record data, if used carefully, to progress the current knowledge in identifying rational prescribing strategies to reduce development of antimicrobial resistance.

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PREFACE

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Ethics Statements

Chapter 2

The baseline antibiotic prescribing audit was approved by the Oxford University Hospitals Clinical Audit Service. Mortality and admission comparisons over 2012-2014 were an approved analysis within the Infections in Oxfordshire Research Database (IORD), which has generic Research Ethics Committee (14/SC/1069), Health Research Authority and UK Health Research Authority (5-07(a)/2009) approval as an anonymised database without individual informed consent. The Infectious Diseases Physician gave consent to be identified in this data, and for the prescribing outcome analysis to be performed.

Chapter 3

The review of Charlson comorbidities was performed on data from the antibiotic prescribing audit, and the review of coding was performed as an audit registered with the Oxford University Hospitals Clinical Audit Service.

Chapter 4

The review of endocarditis cases 2010-2016 was performed as part of a clinical audit approved by the Oxford University Hospitals Clinical Audit Service, and used data from an NHS data warehouse. The 1999-2016 analysis was conducted using an anonymised extract of linked admissions to and microbiology data from the Oxford University Hospitals NHS Foundation Trust from IORD which has generic Research Ethics Committee (14/SC/1069), Health Research Authority and Confidentiality Advisory Group (ECC5-017(A)/2009) approvals. The Leeds analysis was conducted as a service evaluation exercise and approved by the local cardiology audit lead.

Chapter 5

The study was performed using data from IORD which has generic Research Ethics Committee (14/SC/1069), Health Research Authority and Confidentiality Advisory Group (ECC5-017(A)/2009) approvals.

Declarations and attributions

I, Nicola Fawcett, designed and conducted all the analyses presented in this thesis.

A detailed description of work undertaken and assistance obtained is set out below.

Chapter 2

I designed the study, collected the data and authored the manuscript under the supervision of Prof. Sarah Walker and Prof. Tim Peto. Dr Nicola Jones contributed to the design of the study and data analysis method. Dr Vikash Mistry contributed to data collection. Phuong Quan contributed to data collection from hospital databases and statistical data analysis. Prof. Tim Peto and Prof. Derrick Crook contributed to study design and data analysis. Prof. Sarah Walker contributed to study design, analysis, statistical guidance and manuscript preparation. Chris Middlemass and Sheila Weston from the Oxford University Hospital NHS Foundation Trust clinical coding department provided input into the clinical coding process.

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Fawcett N, Young B, Peto L, Quan TP, Gillott R, Wu J, et al. 'Caveat emptor': the cautionary tale of endocarditis and the potential pitfalls of clinical coding data-an electronic health records study. BMC Med. 2019;17(1):169.

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Quan TP, Fawcett NJ, Wrightson JM, Finney J, Wyllie D, Jones N, et al. Increasing burden of community-acquired pneumonia leading to hospitalisation, 1998-2014. Thorax. 2016;71(6):535-542.

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Abbreviations

A. baumanii	Acinetobacter baumanii
aRR	Annual Rate Ratio
CI	Confidence Intervals
CDC	Centers for Disease Control
C. difficile	Clostridium Difficile
CRP	C reactive protein
DCIS	Ductal carcinoma in situ
DDD	Defined Daily Doses
DOT	Days on therapy

E. coli	Escherichia coli
ED	Emergency Department
ESBL	Extended Spectrum Beta-Lactam Resistant
GPA	Granulomatous polyangiitis
H. pylori	Helicobacter pylori
HES	Hospital Episode Statistics
ICD-10	International Classification of Diseases 10th Revision
ICU	Intensive Care Unit
IDP	Infectious Diseases Physician
IDSA	Infectious Diseases Society of America
IORD	Infections in Oxfordshire Research Database
IQR	Interquartile Range
IV	Intravenous
IVDU	Intravenous drug user
K. pneumoniae	Klebsiella pneumoniae
LOS	Length of stay
LOT	Length of Therapy
LR	Likelihood ratio
LRTI	Lower respiratory tract infection
MDR	Multi-drug resistance
MIC	Minimum Inhibitory Concentration
MRSA	Methicillin Resistant Staphylococcus Aureus
MSSA	Methicillin Susceptible Staphylococcus Aureus
NA	Not applicable

NIS	Nationwide Inpatient Sample
NPV	Negative Predictive Value
NHS	National Health Service
OPCS-4 Codes	Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures 4th Revision
OR	Odds Ratio
OUH	Oxford University Hospitals
PCT	Procalcitonin
PPM	Permanent pacemaker
PPV	Positive Predictive Value
P. aeruginosa	Pseudomonas aeruginosa
PSNP	Penicillin non-susceptible *S. pneumoniae*
PSS2	Patient Safety Server 2
RR	Risk Ratio
SD	Standard Deviation
SIRS	Severe Inflammatory Response Syndrome
SLE	Systemic Lupus Erythematosus
S. pneumoniae	*Streptococcus Pneumoniae*
TOE	Transesophageal Echocardiogram
TTE	Transthoracic echocardiogram
VGS	Viridans group Streptococcus
VRE	Vancomycin-resistant Enterococci
UK	United Kingdom
UTI	Urinary tract infection

WCC	White cell count

1 CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

1.1.1 The conflicting priorities of antibiotic use in the acute medical setting

Acute medicine addresses the immediate and early specialist management of adult patients with a wide range of medical conditions who present in hospital as emergencies[1]. In the UK, patients will be admitted to the acute medical specialty either from the Emergency Department, or directly from the community, having been referred in by primary or community care services.

Some patients will have clear evidence of an infection, such as a painful, red leg with a fever, or a cough with green sputum and evidence on a chest radiograph of pneumonia. However in a substantial proportion of patients, the diagnosis may not be clear – the patient who arrives more short of breath, whose symptoms may be due to fluid on the lungs, or infection, or both. This is particularly salient in the older adult, who may have the non-specific sequelae of a decompensation of function due to the infection (such as the onset of confusion or weakness leading to inability to mobilise) whilst simultaneously lacking the inflammatory response and fever one would normally expect and rely on to help diagnose infection[2,3].

This means that the decision to start antibiotics is often far from straightforward. The acute medical clinician is required to consider the probability that the patient actually has a bacterial infection, and then make a judgement call about whether in this particular patient, the risks of withholding antibiotic therapy outweigh the risks of giving antibiotics.

There is currently a widespread focus in acute medicine and emergency medicine on emphasising the importance of giving antibiotics promptly in sepsis as part of the "Surviving Sepsis Campaign". This is based largely on retrospective data from patients admitted to intensive care for sepsis, that showed that mortality increased 8% for every hour delay in antibiotic administration after the patient developed hypotension[4]. Other studies have

suggested less dramatic effects[5], and a meta-analysis did not find any overall benefit of rapid antibiotic administration[6]. Further the degree to which these analyses were able to account for confounding by adequacy of clinical care per se is unclear. Nevertheless, in both the UK and worldwide, government bodies and funders have implemented initiatives or penalties designed to drive improved delivery of early antibiotics. Anecdotally, in the acute medical setting in the UK this has driven the balance of decision making towards a perceived large harm of withholding antibiotics in anyone who might possible have an infection and sepsis.

Conversely, in the era where the World Economic Forum annual report on global risks states that "arguably the greatest risk…to human health comes in the form of antibiotic-resistant bacteria"[7], and the World Health Organisation Chief, Margaret Chan, states that resistant bacteria mean "an end to modern medicine as we know it"[8], there is an increasing focus on reducing use of antibiotics as a means of reducing selection pressure and development of resistance by bacteria. This has led to government-based initiatives incentivising hospitals to reduce volumes of antibiotic use, broad-spectrum antibiotic use[9,10], and substantial resources being invested in measures designed to change antibiotic use.

The physician is thus increasingly being required to make prescribing decisions based not just on the patient in front of them, but also the risk to the population as a whole from future resistant infections[11]. The acute physician has to balance these competing priorities, together with a wide range of other factors that affect the decision to prescribe – such as patient expectations, a perceived validation of illness, and social/societal expectations[12,13].

The focus of this D.Phil. is to examine and progress the current knowledge available to the acute medical physician in choosing antibiotic prescribing strategies that are most likely to be effective in reducing the spread of antimicrobial resistance, whilst still being safe for the patient.

In the first part of this Introduction, I will first look at the dilemma of diagnosing infection, and the degree to which one can use objective criteria to guide the physician in ruling in or out bacterial infection, and assist the antibiotic prescribing decision.

In the second part, I will look at the currently-available evidence for particular prescribing strategies in terms of both resistance selection and clinical effectiveness – exposing fewer patients to antibiotics, changing the duration of course, or doses given. I will then look at existing interventions to change antibiotic use in hospitals, and their effect on resistance, at each stage considering the implications on strategies the acute medical physician may use.

I will then present my thesis plan, aiming to progress the current knowledge around antibiotic use in the acute medical setting, and resistance selection.

1.2 How easy is it to diagnose infection?

For the hospital physician, the most common bacterial infections seen are respiratory tract infections (pneumonia, bronchitis, infective exacerbations of asthma/pulmonary disease) urinary tract infections or pyelonephritis, skin/soft tissue infections, infective gastroenteritis, and sepsis of unknown source[14].

For the majority of infections seen in hospitals, clinical guidance emphasises that diagnosis is based on a constellation of clinical features, combined with diagnostic tests, to form a clinical diagnosis. Strategies that enable the physician to reliably and accurately identify patients who do not need antibiotics would be of great assistance in assisting the clinician who aims to minimise antibiotic exposure without putting patients at risk of under-treatment.

1.2.1 Use of validated objective criteria to rule in or rule out bacterial infection in the acute hospital setting

There are a few good examples where clinical criteria do exist to rule out infection. One is the CENTOR criteria to rule out streptococcal pharyngitis, whereby in patients presenting with a sore throat, the absence of tonsillar signs, tender cervical lymph nodes, pyrexia, presence of cough, and age >14 years means that there is a lower than 2.5% chance of streptococcal throat[15,16]. However this is a largely primary care presentation.

The Duke Criteria for Endocarditis are used to diagnose endocarditis. Briefly, this guidance identifies major criteria (such as repeated blood cultures positive for typical microorganisms and echocardiographic demonstration of valvular involvement), and minor criteria (such as fever, predisposing factors, limited microbiological evidence and other systemic features). Definite cases fulfil 2 major criteria, 1 major criterion and 3 minor criteria or 5 minor criteria. Possible cases fulfil 1 major criterion and 1 or 2 minor criteria, or 3 minor criteria. In their original paper, Durack et al[17] showed that in a review of 421 patients with suspected endocarditis, of the 52 who failed to meet the criteria, none subsequently had pathologically proven endocarditis (based on microscopy showing and infected valve) or a clinical diagnosis. After a subsequent modification, the updated criteria[18] were shown to have a negative predictive value (NPV) of at least 92% by Dodds et al[19] in a study of 405 episodes of infective endocarditis (one patient who did not fit criteria had possible endocarditis at autopsy, and five had in-hospital deaths). Data on sensitivity/specificity of the Duke criteria is limited, as definitive confirmation of infective endocarditis relies on histological examination of the valve, which is only feasible if the patient has cardiac surgery to replace the valve, and only happens in a minority of patients, who may not be representative of the wider population of patients who have suspected endocarditis. One study of patients treated surgically for suspected endocarditis found that in a total 581 episodes of illness the

sensitivity of Duke criteria for definite infective endocarditis was 72% (95% CI 66-77%) and specificity 74% (95% CI 58-87%)[20], which broadly matches other studies[21,22]. They did not assess the predictive ability of Duke criteria for possible infective endocarditis.

Whilst this thesis focuses on evidence for the use of antibiotics in the acute medical (adult) setting, it is also worth mentioning the Rochester Criteria for febrile infants <60 days age. In the presence of 12 criteria (such as lack of previous hospitalisations, chronic or underlying illness, and otherwise appearing well) the risk of serious bacterial infection was less than 1%[23,24].

However these conditions are the exceptions, rather than the rule, when it comes to guidance for the clinician in objectively being able to rule out bacterial infection.

As an illustrative example, hospital-based clinical guidelines in Oxford clearly state the diagnosis of urinary tract infection (UTI) should only be made in the presence of lower urinary tract symptoms (frequency, dysuria, urgency, lower abdominal discomfort) in combination with positive urinalysis (presence of nitrites with or without leucocytes in the urine.

In an excellent study of predictive values of clinical features or objective scores, Little et al[25] assessed the predictive value of clinical scores and dipstick results to predict UTI in patients presenting with possible UTI to primary care. Having identified the clinical criteria with higher likelihood ratios (LRs) and creating a combined score, they found that the presence of urine cloudiness, dysuria and nocturia had a positive predictive value (PPV) of 82%; absence of all three had a NPV of 67%. A urinalysis showing nitrites, and either leucocytes or blood had a PPV 92%; urinalysis negative for nitrites, leucocytes and blood had a NPV of 76%. (It is worth noting that in this study, UTI was defined as bacteruria $>10^3$ colony-forming units per ml of growth on agar culture medium alone, and did not specify additional clinical

criteria. Thus patients with 'asymptomatic bacteruria' i.e. harmless colonisation of the urine with bacteria would have been classified as a UTI.) The authors stated "clinicians can be reasonably confident that patients with suspected UTI who have dysuria, nocturia and cloudy urine do have a UTI, but they should be cautious about excluding patients based on the absence of these features". A systematic review[26] of the predictive ability of symptoms and signs to diagnose UTI[26] looked at 16 studies incorporating 3,711 patients, and again concluded that "individual symptoms and signs […] have a modest ability to 'rule in' or 'rule out' the diagnosis of UTI.

The problem is even more difficult in the older adult, who may not be able to give a clear clinical history, is more likely to be confused, and more likely have a compromised immune system and be unable to mount a systemic inflammatory response. In a UK study of older adults with concordant positive blood and urine cultures (clinically bloodstream infection due to urinary tract infection), 38/61 (62%) entirely lacked lower urinary tract symptoms[27]. Similar results have been seen in other studies[28]. Equally, given the relatively high prevalence of asymptomatic bacteruria, a urine culture cannot be relied on alone.

1.2.2 **Predictive ability of expert consensus criteria defining infection**

There are collections of reports of expert consensus in objective criteria for infection, but there is limited data on their overall accuracy in diagnosing infection. For instance, the Centre for Disease Control and Prevention (CDC) publishes criteria by which it defines infection at body sites, for the use of defining reportable healthcare-associated infection[29]. The primary aim of these criteria is to have a standardised set of criteria for reporting, rather than to accurately diagnose or exclude infection. A consensus conference in 2001 aimed to develop criteria for initiation of antibiotics for residents in long term care facilities - based on expert

opinion, a set of criteria for UTI, lower respiratory tract infections (LRTIs), skin/soft tissue infection and fever of unknown origin were created, termed the 'Loeb criteria'[30]. However, even when using these expert consensus definitions, their ability to either predict or rule out infection is limited.

For example, a study of 424 older adults[31] presenting to the emergency department subsequently evaluated the Loeb criteria in terms of its ability to rule out significant bacterial infection. The presence of a bacterial infection was defined retrospectively by concordance between two physicians in a Likert-scale assessment of 4 or 5 (out of 5) and was felt to be present in 77 patients. Loeb criteria identified 42/52 patients with respiratory/urinary/skin/soft tissue infection, and CDC criteria 43/77 patients with any bacterial infection. Whilst specificity of these criteria were high (0.99 for both), sensitivity was variable. The Loeb criteria performed particularly poorly for UTIs with sensitivity of 0.26; for LRTIs and skin/soft tissue infections, sensitivity was 0.50 and 0.87 respectively. It is worth noting that Emergency Department (ED) physicians performed similarly – in 44 cases ED and gold standard were in agreement, in 33 cases the ED physician missed the infection, and in 27 cases infection was diagnosed which was not supported by results.

Another issue is that even if there are criteria, there may be a lack of clarity whether the criteria are present due to the infection being assessed or another pathology. As an illustrative example, a study asked two physicians trained in geriatric medicine to retrospectively classify 154 older hospitalized patients with bacteriuria as either urinary tract infection or asymptomatic bacteriuria. Despite using the same criteria, in 30 (19%) of cases there was disagreement, driven mostly by lack of agreement on whether systemic symptoms (e.g. delirium or fever) were due to a urinary infection or a concurrent infection at another site[32].

In summary, there are few validated objective criteria exist that effectively rule out bacterial infection in the acute medical setting, to the point where the acute clinician can use them as a guide when not to use antibiotics.

1.2.3 Use of laboratory testing to enhance decision making around antibiotics

There is no single definitive biochemical test that can rule in or out a bacterial infection. Current hospital practice in diagnosing infection focuses on the use of white cell count (WCC), neutrophils, and C Reactive Protein (CRP) levels. None of these can independently be used to definitively rule infection in or out, but they can be used as a supplement to clinical assessment to guide antibiotic prescribing[33]. Despite a worldwide focus on encouraging the development of definitive point-of-care tests that can diagnose bacterial infection, from strategy documents[34,35] to the Longitude prize, there remains no single test that the acute clinician can use to completely guide the prescription, or withholding, of antibiotics.

One of the more recognised biomarkers being assessed as a potential assay to help guide antibiotic decision making is procalcitonin (PCT) – low levels are generally predictive of a non-bacterial infection. In a systematic review comparing PCT and CRP as markers for bacterial infections, PCT had a sensitivity of 0.88 (95% confidence interval (CI) 0.80-0.93) vs 0.75 (95% CI 0.56-0.77) for CRP, and a specificity of 0.81 (95% CI, 0.67–0.90) vs 0.67 (95% CI 0.56–0.77) respectively[36].

Initial trials of introducing procalcitonin testing to hospital suggested that it had the potential to reduce antibiotic prescribing without adverse clinical outcomes in patients with respiratory tract infections.

For example, Schuetz et al[37] in the ProHOSP trial randomised 1359 patients presenting to emergency departments with a chest infection to either a PCT-based antibiotic prescribing algorithm or standard guidelines. They found a lower duration of antibiotic exposure in the PCT group, with no evidence of increases in adverse outcomes. Similar results were obtained in a smaller study of 302 patients by Christ-Crain et al[38], which randomised patients to usual care or a PCT test with guidance of antibiotics being "strongly discouraged" to "strongly encouraged" based on PCT level. De Jong et al[39]randomised 1575 admissions to an intensive care unit to two similar strategies, and showed that using PCT to guide discontinuation of antibiotic therapy reduced length of treatment without evidence of increases in adverse outcomes.

Conversely Huang et al[40] studied 14 emergency departments in the US, and found that in real-life practice, the effect on antibiotic usage was minimal. They specifically focused on LRTIs where the "treating clinician had given an initial diagnosis of acute lower respiratory tract infections but had not yet decided to give or withhold antibiotics […] such that PCT data could influence the prescribing decision". They looked at 1656 patients, randomising 826 to have PCT testing with the result revealed to the clinician, and 830 to usual care (with PCT taken but not revealed). They found that there was no difference in duration of antibiotic treatment (median 4.2 days with PCT and 4.3 days with standard care). This was largely due to many patients in the usual treatment arm with a low PCT not receiving antibiotics anyway, and in increase in antibiotic prescribing for patients for whom the physician saw a high PCT compared to the 'unrevealed' group. There is currently a significant focus on point-of-care testing to help diagnose infection, indeed the Longitude Prize is currently on offer for the development of a cheap, accurate, paid and easy-to-use point of care test kit for bacterial infections. There are a number of other candidate biomarkers for use in improving the diagnosis of bacterial infection, and subsequent antibiotic use, such as serum amyloid A.

Other technologies proposed for this purpose include the use of bacterial DNA sequencing, and transcriptomics/proteomics/metabolomics of either the pathogen or host response. None of these currently have enough clinical data to support their use, though are under development[41].

In conclusion, whilst biomarkers, including procalcitonin, are of assistance in assessing the likelihood of bacterial infection, their current performance suggests that the best they can do is to enhance, rather than potentially replace, the diagnostic process.

1.3 Reviewing current evidence base for reducing antibiotic use and addressing resistance

1.3.1 The association between antimicrobial consumption and resistance

Many of the international reports on antimicrobial resistance[35,42,43] are based on the premise that less prescribing on a national scale will mean less resistance. Data come from a relatively small number of studies (although numbers are increasing).

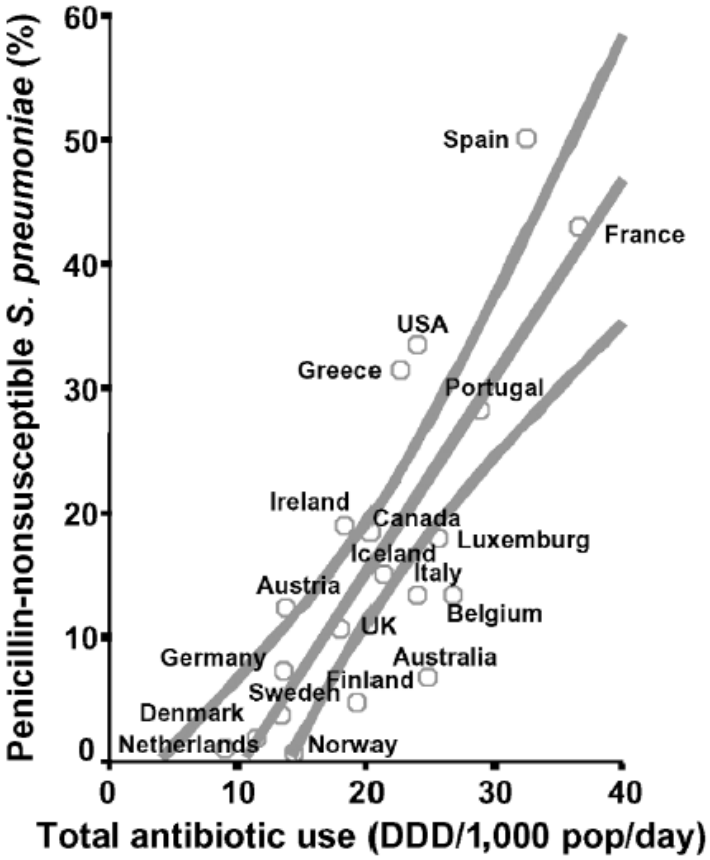


Figure 1. Total antibiotic use in the outpatient setting (vertical axis) versus prevalence of penicillin-nonsusceptible *Streptococcus pneumoniae* (horizontal axis) in 20 industrialized countries. A regression line was fitted with 95% confidence bands ($r = 0.75$; $p < 0.001$).

Figure 1: Antibiotic pressure and Streptococcal resistance, from Albrich et al[44]

For example, Albrich et al[44] assessed the relationship between outpatient antibiotic use and penicillin-nonsusceptible *Streptococcus pneumoniae* and macrolide-resistant *Streptococcus spp*., finding that total antibiotic use was associated with prevalence of non-susceptible *S. pneumoniae*, and macrolide use was associated with macrolide-resistance in *Streptococcus* spp. isolates from microbiology laboratories. **Figure 1** (taken from their paper) shows the apparent association between high-prescribing countries and increased prevalence of penicillin non-susceptible *S. pneumoniae* (PSNP). Both Goossens et al and Riedel et al subsequently showed similar effects between total penicillin use and PNSP prevalence[45,46].

Seppala et al[47] showed a positive association between local erythromycin consumption in 206 health authority areas in Finland and erythromycin resistance rates in Group A Streptococcal isolates[47]. Resistance rates in Group A Streptococcal isolates in Finland suggested that a reduction in outpatient macrolide consumption from 1990 onwards was associated with a reduction in resistance rates[48] (**Figure 2**).

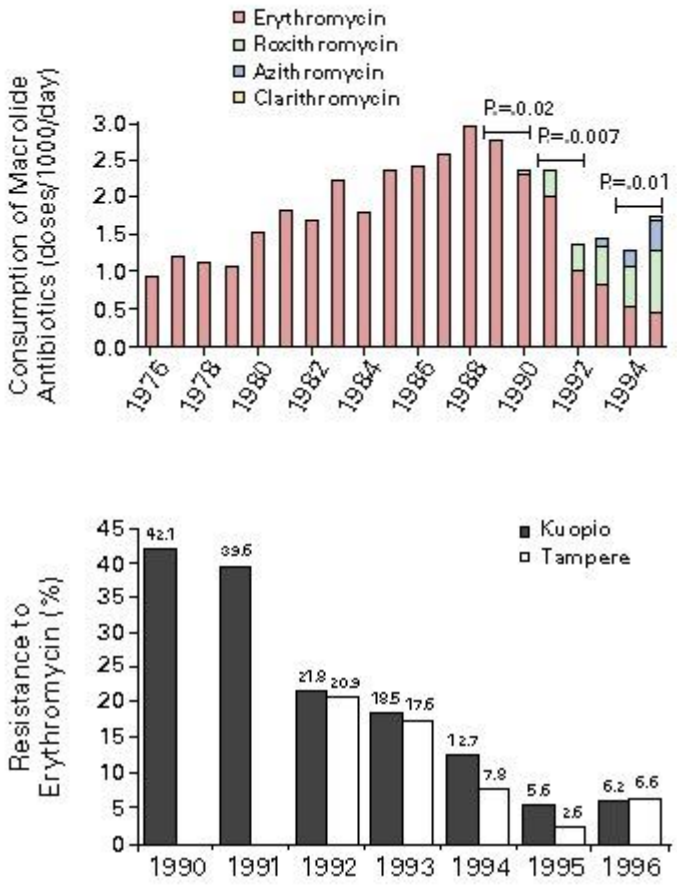


Figure 2: Outpatient consumption of macrolides in Finland and frequency of resistance to erythromycin in Group A Streptococcal isolates in two Finnish laboratories, from Seppala et al [48]

More work has subsequently been done strengthening the association between macrolide consumption and macrolide resistance in *S. pneumoniae*[49]. Additional associations between consumption and resistance in Europe seen by a subsequent study by Goossens et al were

between cephalosporin consumption and penicillin resistance in *S. pneumoniae*, ciprofloxacin consumption and ciprofloxacin resistance in *Escherichia coli*, and co-trimoxazole consumption and co-trimoxazole resistance in *E. coli*[46].

More recently, *Helicobacter pylori* resistance rates to macrolides and quinolones have been shown to be associated with macrolide and quinolone consumption respectively on a national level[50] (**Figure 3**).

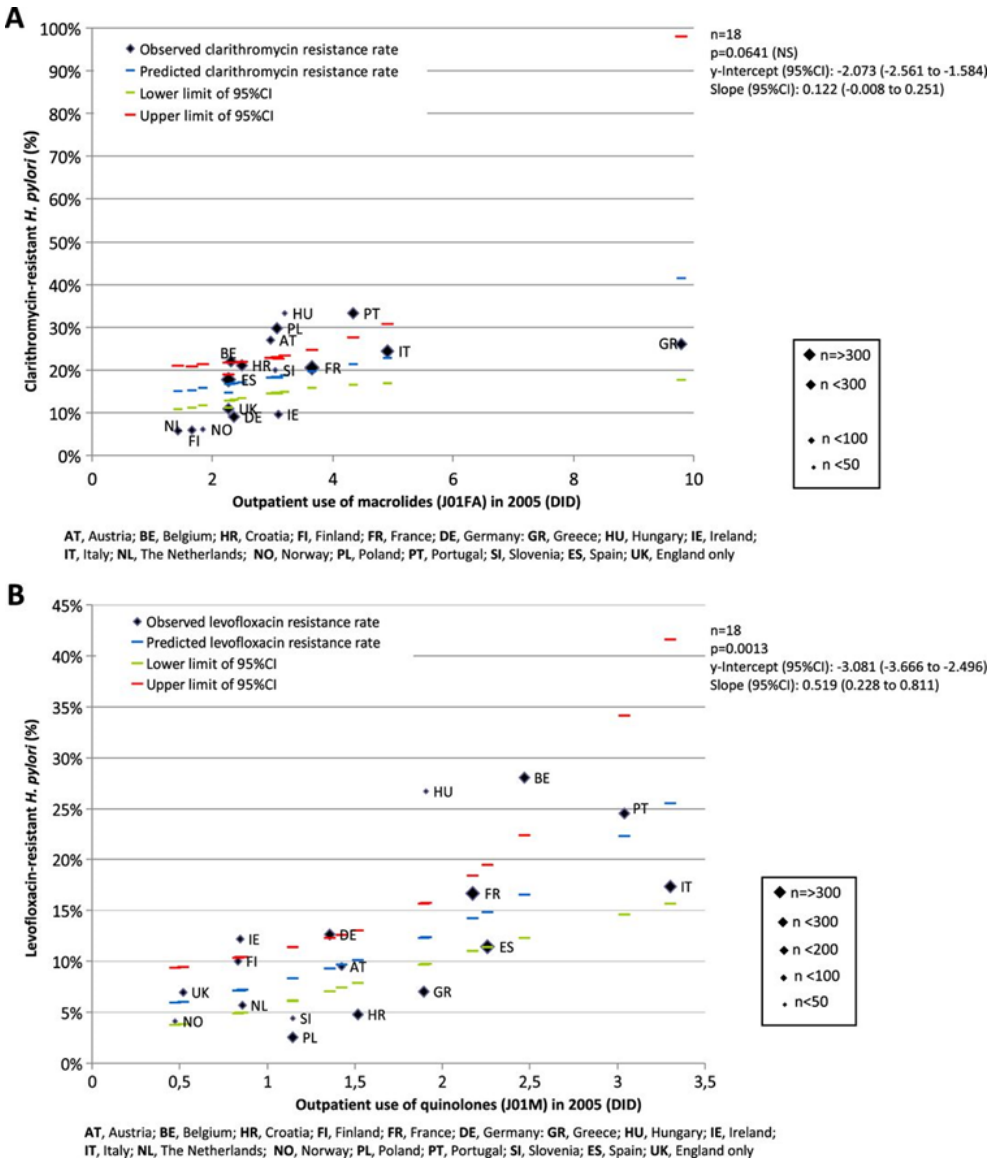


Figure 3: Association between outpatient macrolide and quinolone use and resistance in *H. pylori* strains, from Megraud et al[50]

An interesting study by Bergman et al[51] investigated the association between regional antibiotic consumption and resistance patterns in *E. coli* isolates in Finland 1997-2005. They found significant associations between nitrofurantoin use and nitrofurantoin resistance, cephalosporin use and nitrofurantoin resistance, amoxicillin use and fluoroquinolone resistance, and fluoroquinolone use and ampicillin resistance. They found no association between fluoroquinolone use and fluoroquinolone resistance. A UK study by Pouwels et al[52] investigated associations between primary care prescribing data and *Enterobacteriaceae* grown in urine samples in a national database between 2014-2016. Exploiting geographical variation, they showed that use of trimethoprim and extended-spectrum penicillins was associated with higher rates of trimethoprim resistance, though interestingly nitrofurantoin use was associated with lower rates of trimethoprim resistance. A further study by this group on the same dataset focussed specifically on *E. coli* grown from urine samples and showed a positive association between extended-spectrum penicillin prescribing and resistance to amoxicillin and ciprofloxacin. No association was seen with beta-lactamase-sensitive penicillins. They also found that trimethoprim prescribing was associated with ciprofloxacin resistance[53].

More locally, a study of *E. coli* infections in Oxfordshire 1998-2016 found an association between co-amoxiclav resistance in *E. coli* from urinary tract infections with co-amoxiclav consumption in the patient's local primary care facilities[54].

A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance by Bell et al[55], conducted in 2014 and including 243 studies, supported the overall association between consumption and resistance, finding that there was an increased likelihood of studies finding an association if they looked at tetracycline-resistant *S. pneumoniae*, quinolone-resistant *E. coli*, and studied both adults and children. Studies that investigated beta-lactam consumption or Methicillin Resistant *Staphylococcus Aureus*

(MRSA) tended to find a weaker relationship. Southern European countries appeared to produce stronger associations between consumption and resistance. They concluded that when they analysed associations with resistance by bacterial genus, positive relationships between consumption and resistance were only obtained for enteric bacteria and *Streptococcus* spp. They highlighted the lack of studies overall that looked for co-selection as a phenomenon (whereby antibiotics of one class can drive selection for resistance to another class of antibiotics, similar to the associations found by Pouwels et al[52,53]).

Whilst these studies certainly provide strong evidence that overall consumption may drive development and spread of resistance, they have a number of caveats, the most important being that the majority are based on ecological comparisons of populations rather than individual level analyses. Other hypotheses include differing patterns or prevalence of infections caused by the local climate[56], or population density[57], of an area, driving both prescribing and ease of transmission and spread of resistance.

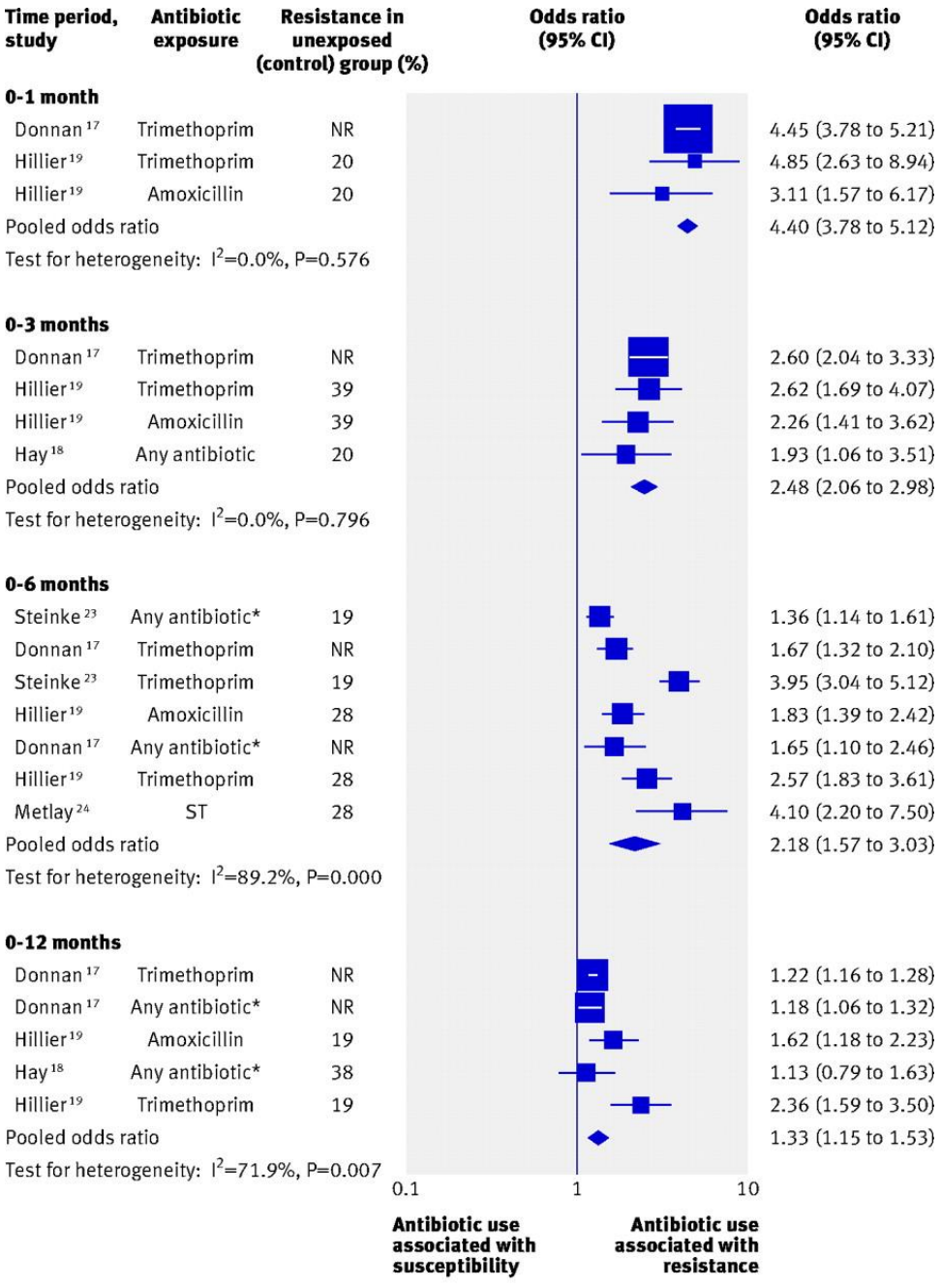
However, by identifying the associations that have been repeatedly, and most strongly, found, these studies can assist in potentially identifying antibiotic/resistance associations for which interventions to change prescribing may have a higher success of affecting resistance rates.

1.3.2 **Prior antibiotic exposure as a risk factor for resistant infection**

The association between antibiotic use and resistance is more compelling when analysed at an individual patient level, where there are numerous meta-analyses demonstrating the link between prior antibiotic exposure and infection or colonisation with resistant organisms[58-63].

In one of the best examples summarising this association, a systematic review and meta-analysis of studies that assessed the risk of resistant infection based on prior primary care antibiotic exposure, Costelloe et al[64] looked at 24 studies of urinary tract and respiratory tract

infections (**Figure 4**). They concluded that there was a significant association between prior antibiotic exposure and subsequent resistance, with the stronger associations seen when the exposure was more recent, but the association persisting in studies where the exposure was up to 12 months prior to the infection.



* Any antibiotic other than trimethoprim. ST=sulfamethoxazole-trimethoprim. NR=not reported

Figure 4: The association between prior antibiotic exposure and resistant infection in a meta-analysis by Costelloe et al[64]

In all, there is therefore relatively compelling evidence that avoiding exposing patients to antibiotics is effective in reducing that patient's subsequent risk of resistant infection.

1.3.3 **Clinical strategies to start fewer patients on antibiotics**

Given this, it is uncontroversial to suggest that strategies that reduce the number of patients exposed to an antibiotic are likely to be beneficial in reducing the spread of antimicrobial resistance.

There are many studies suggesting that up to a third of antibiotics prescribed in hospitals may be inappropriate[65], and therefore that there is potential for significant reductions in prescribing without adverse effects. It is worth noting, however, that many of these studies assessed antibiotic use in volume, and that reductions in total use could come from both shorter durations of courses as well as fewer patients being started on them.

In primary care, there have been significant reductions in antimicrobial prescribing achieved in the UK over recent years, attributed in part to significant efforts to reduce 'inappropriate' use of antibiotics for conditions where there is an evidence base that antibiotics are of little or no benefit (mainly uncomplicated respiratory tract infections such as bronchitis without complications)[66,67]. It is not unreasonable to consider that similar reductions in antimicrobial prescribing may be achievable in the acute hospital setting. However, as discussed above, the diagnosis of conditions presenting for acute medical care is often not straightforward, and the physician is asked to make a clinical judgement call of the likelihood of misdiagnosis, and the risk of delays in treatment if an antibiotic-requiring condition is the correct diagnosis, compared to the benefits of avoiding unnecessary antibiotics. In the acute setting, the patient will already have been referred by a primary care specialist or emergency department, and will thus already either have higher uncertainty, a higher probability of serious infection, or

be more at risk of rapid deterioration. However the hospital physician has access to more tests to inform the diagnosis.

There are a few conditions where strategies to reduce prescribing in the acute hospital setting without adverse effect have been effective.

A Cochrane review of interventions to change antimicrobial prescribing in hospitals by Davey et al[68] is discussed more completely later in this Chapter. Of the 18 studies which targeted antibiotic exposure as an outcome, 8 specifically looked at reducing the percentage or risk of patients being started on an antibiotic, and all of these used PCT testing[38,69-75]. One further study was included in the review which targeted "% patients treated" and this was the only one which aimed to reduce patients started on an antibiotic without the use of PCT testing.

Specifically, Hadi et al[76] used an educational intervention to change antibiotic prescribing in patients with a fever presenting to the medical department of an Indonesian hospital, measuring antibiotic use before, during, and after an educational intervention. As part of a wider set of recommendations and encouragement to take blood cultures, they recommended that patients with a fever who did not fulfil the Severe Inflammatory Response Syndrome (SIRS) criteria[77], and did not have a clear source of infection, received antipyretics, blood cultures and daily checks, but no antibiotic therapy. They found a significant reduction in antibiotic use, and fewer patients with these criteria started on antibiotics after initiation of the guideline. The main reduction in antibiotic use was not giving antibiotics to patients diagnosed with Dengue fever. They saw no large changes in mortality rates. However in the first six days following implementation six patients diagnosed with sepsis died, and three patients diagnosed with probable Dengue infection died, of which one had received

antibiotics. They noted that Dengue mortality is quoted at <1%. There was no measurement of impacts on resistance.

There is more evidence from studies looking at prescribing in emergency departments, which share significant overlap in patient presentations with acute medical admissions. A number of studies have demonstrated the effectiveness of interventions to reduce antibiotic prescribing for respiratory tract infections, such as uncomplicated acute bronchitis, where there is good evidence that antibiotics do not significantly improve clinical cure rates[78].

As two recent examples, Yadav et al[79] conducted a cluster randomised-controlled trial in five emergency departments and four urgent care centres. They studied antibiotic prescribing during the 2016/2017 and 2017/2018 'flu seasons' (November to February), and found that targeted education interventions reduced 'inappropriate' prescribing for respiratory tract infections by 33%. However, it was noted that this represented a decrease in overall prescribing by a modest 0.7% due to the low baseline inappropriate prescribing rate.

Madran et al[80] studied the effect of implementing a guideline for the treatment of respiratory tract infections in a Turkish tertiary care centre using an uncontrolled before/after study design. They looked at the appropriateness of antibiotic prescriptions in April 2017 compared to the same period in the preceding year, and saw a decrease in both inappropriate prescriptions and the number of patients started on antibiotics from 49% to 29%.

The other clinical condition for which there is increasing focus on reducing antibiotic exposure in the inpatient medical setting is the management of asymptomatic bacteruria. There is increasing evidence that, in the absence of symptoms, in the non-pregnant patient, antibiotic treatment of patients with positive urine cultures is not associated with improved clinical outcome[81], and may even increase risk of subsequent urinary infections as well as subsequent resistance[82]. There are now a number of studies showing the effectiveness of

educational interventions on reducing treatment of asymptomatic bacteruria[83-85], and reducing treatment of the condition has become a national focus in England[86].

It is worth highlighting that in the vast majority these studies, there was no analysis of clinical outcome or resistance rates, and the success was judged based on compliance with guidance. Nevertheless, together the studies suggest that there is some scope to attempt to reduce prescribing in the acute setting, though it is probably best targeted at particular presentations where antibiotic prescribing persists despite good evidence that antibiotics are not associated with improved outcome.

1.3.4 **Delayed antibiotic prescribing strategies**

One method of dealing with patients for whom there is genuine clinical uncertainty about the benefit of antibiotics that has been trialled in primary care is the use of delayed prescribing. In this, a prescription is made available to the patient (either immediately, immediately and post-dated or for collection at a later date), and the patient is given advice to not start antibiotics immediately but that if symptoms get worse or do not improve, then antibiotics can be initiated without the need for further appointments. In the most recent Cochrane meta-analysis of delayed prescribing strategies for respiratory tract infections, where the vast majority of trials have been focused, Spurling et al[87] concluded that for acute respiratory infection, delayed prescribing was associated with reduced antibiotic use whilst maintaining patient satisfaction and clinical outcomes. For acute otitis media and sore throats, there was a modest improvement in symptoms for immediate vs delayed prescribing, but similar patient satisfaction and complication rates.

To date, no trials of delayed prescribing have been conducted in secondary/tertiary care. It is interesting to note than when searching for such trials, the top results all related to studies

looking at adverse clinical outcome in patients who receive delayed antibiotics for infection. As discussed above, one issue with attempting to transfer this strategy to hospital care is that the patients presenting are more likely to have a severe infection and be at increased risk of harm from delayed treatment. Additionally, given the significant focus on emphasising the adverse impact of delaying antibiotics in patients with sepsis[5,9], it is a more challenging environment to try and implement delayed prescribing.

Nevertheless, it is reasonable to consider whether there are patient groups where there is genuine uncertainty about the benefit of antibiotics in whom delayed antibiotics could be trialled, such as the older patient with acute functional decline who has no objective evidence of infection. To do so in the acute hospital setting with patients at higher risk of deterioration may require closer monitoring than that used in primary care, which is reliant on patient/carer-based escalation in case of deterioration, or at most a daily review.

1.3.5 **Altering duration of antibiotic treatment to reduce resistance**

1.3.5.1 ***Should we be aiming at shorter or longer courses in acute medicine?***

In the 2008 Maxwell Finland Lecture[88], Louis Rice proposed reducing overall antibiotic use by shortening duration may be the change most palatable to clinicians, given the difficulty in trying to encourage non-prescription when there is increasing evidence of the adverse effects of delaying antibiotics when needed. The rationale is that the longer antibiotics are given, the longer bacteria are put under selective pressure, and the more likely they are to either develop spontaneous resistance mutations, or undergo horizontal gene transfer. Additionally the ecological effects of antibiotics on the microbiota of the human body would be hypothesised to be greater the longer they are taken for, whereby resistant bacteria expand with concurrent suppression/removal of susceptible strains. The converse stance, which has been historically

raised as a reason to ‘always finish your course’, is that shorter courses may allow incomplete suppression of the pathogen, resulting in persistence of the most resistant bacteria. This concept has been attributed first to Sir Alex Fleming in his Nobel Prize lecture in 1945[89] where he quotes:

“Here is a hypothetical illustration. Mr. X. has a sore throat. He buys some penicillin and gives himself, not enough to kill the streptococci but enough to educate them to resist penicillin. He then infects his wife. Mrs. X gets pneumonia and is treated with penicillin. As the streptococci are now resistant to penicillin the treatment fails. Mrs. X dies. Who is primarily responsible for Mrs. X’s death? Why Mr. X whose negligent use of penicillin changed the nature of the microbe. Moral: If you use penicillin, use enough.”

However in this case, his prior passages refer not to duration of course, but size of dose:

“There may be a danger, though, in under dosage. It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body. The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant.”

Nevertheless, for decades the public health message has been that incomplete courses of antibiotics can encourage resistance to develop[90], rather than that suboptimal doses can encourage resistance, with apparently very little evidence to support this outside the treatment of staphylococcal disease and tuberculosis, where mutation and persistence of the infecting pathogen are major mechanisms of resistance development.

For most other pathogens, especially the Enterobacteriaceae, the most important mechanisms of resistance development are increasingly seen as being due to large scale ecological effects of antibiotic selection pressure in the environment, in other animals receiving antibiotics, especially farm animals, at a population level, and at the level of the host microbiota. In this model, any reduction in selection pressure would be hypothesised to reduce development and spread of resistance.

I will review the evidence for duration of antibiotics in common clinical conditions encountered by acute medical physicians, acknowledging that there is limited generalisability to rarer and more specialised conditions, which would generally be treated with the input of microbiology/infectious diseases specialists.

1.3.5.2 *Shorter courses - evidence on clinical outcome*

There is increasing evidence that it is possible to use shorter courses of antibiotics to treat infections. The seven-day courses which have been the norm for the last few decades appear to come largely from the initial antibiotic trials. In these, seven days were chosen as duration, apparently fairly arbitrarily as it represented a full week, and was the approximate length of time required for the patient to feel better, with 14 days chosen for more 'serious' infections. Thus were standard antibiotic courses settled upon, based largely on the definition by Emperor Constantine in AD 321 that a week would represent 7 days, to fit the Christian practice of a rest day every seventh day.

It is important to acknowledge that these trials were conducted in an age where there was very little focus on minimising antibiotic exposure, and extensive trials to try and identify the shortest possible effective treatment course could be seen as therefore unnecessary. In more

recent years there have been more trials studying clinical outcome (either bacteriological cure or clinical cure) with shorter courses.

An overview of systematic reviews available for the treatment of primary care infections was published by Dawson-Hahn[91] et al in 2017, and is discussed here given the high degree of overlap in conditions included and those encountered by the acute medical physician. This overview concluded that for all conditions studied, there was no evidence of difference in clinical outcome with shorter courses compared to longer courses. In adults they studied acute bacterial sinusitis (3-7 days vs 6-10 days), uncomplicated urinary tract infections (3 days versus 5 or more days), pyelonephritis (7-14 days vs 14-42 days), community-acquired pneumonia (7 or fewer days versus 8 or more days), and urinary tract infections in older women (3-6 days vs 7-14 days).

A similar overview of systematic reviews assessing treatment of secondary care infections by Onakpoya[92] et al found no evidence for a difference in clinical outcome with shorter versus longer courses. They studied peritonitis (3-5 days vs 10-14 days), pneumonia (3-7 days vs 8-10 days), hospital-acquired pneumonia (7-8 days vs 10 or more days), pyelonephritis/sepsis with urinary tract infection (7 vs 14 days and 7 vs 28 days) and intra-amniotic infection (single vs multiple dose). They highlighted that the quality of evidence was often low, and felt overall that there was limited evidence that currently weakly supports shorter durations of antibiotic therapy.

It is interesting to consider that it may be possible to reduce antibiotic durations even more than the current '3-5 days' view of a short course. Indeed, early antibiotic trials for pneumonia studied single dose treatment[93] with apparent good treatment response.

Conversely, the only common infection seen in primary and secondary care where a meta-analysis suggests benefit from longer courses is in acute otitis media, where a Cochrane

review conducted by Kozrskyj et al[94] suggested that treatment failure was higher in patients treated with 2-6 days' antibiotics compared to 7 days or longer (20.5% vs 17.5%, NNT 28 (17-77), judged very low quality evidence.

Since these overviews/reviews, there has been one more recent, and very relevant double blinded placebo-controlled randomised controlled trial by Cranendonk et al. studying 6 days vs 12 days antibiotic treatment for patients hospitalised for cellulitis, which awaits publication but was reported as a conference abstract in 2018. They found that whilst there was no difference relapse-free cure rates at 60 days, at 90 days relapse rates were 23.5% in the 6 day group vs 6.0% in the 12 days group (p=0.04, confidence intervals (CI) not given). They noted that compared to a previous study by Hepburn et al[95], which compared short (5 days) vs long (10 days) treatment, and found no difference, their population was older and more comorbid, suggesting some need for risk stratification for short course therapy, and that older adults may benefit from longer courses. Possible reasons for this may be reduced antibiotic delivery to sites of infection due to poor cardiac function or vascular supply, or the impaired immune response seen with age 'immune senescence'. Additionally, they are more likely to be colonised with resistant organisms. However it is also worth noting that older adults will also be at higher risk of antibiotic-related complications[96].

1.3.5.3 ***Shorter vs longer courses- effect on resistance***

The reviews by Dawson-Hahn[91] and Onakpoya[92] both highlighted the lack of information available regarding the impact of treatment duration on antimicrobial resistance, due to poor or absent reporting of this outcome.

The most comprehensive studies appear to come from the intensive care environment studying the treatment of ventilator-acquired pneumonia. This is probably because patients in

this setting have microbiological samples taken routinely and regularly, making both identification of initial pathogen, and follow up of microbiological outcome, more straightforward.

Singh et al[97] studied 81 patients with ventilator-associated pneumonia, comparing short course ciprofloxacin, which was discontinued at 3 days provided the risk score remained low, compared to conventional practice of 10-21 days of treatment. Mean duration of treatment was 3.0 days vs 9.8 days, with antibiotics continued beyond 3 days in significantly fewer patients in the short course treatment arm (11/39 28% vs 34/39 97%, p=0.001). They found no difference in mortality 5/39 13% vs 13/42 31% p=0.06 in short vs standard groups) or recurrence (though the size of study means that only very large differences would be detected), and shorter overall stay in the intensive care environment with the short course ciprofloxacin). They found a lower rate of subsequent reinfection with a resistant isolate in the short course group (14% vs 38% p=0.017), with resistant organisms being P. *aeruginosa*, Enterobacteriaceae, *Enterococcus* species, MRSA and *Candida* species.

Chastre et al[98] conducted a randomised, double blinded trial of 197 patients with ventilator acquired pneumonia, treated with either 8 or 15 days of antibiotics, and found no evidence for excess mortality or recurrent infection with the shorter course. However the patients with infection caused by *P. aeruginosa* had a higher recurrence rate (40.6% vs 25.4%; difference 15.2%, 95% CI 3.9-26.6%). They found that, of the patients who did have recurrent infections overall, resistant pathogens were less commonly found in the shorter course group (42% vs 62%, p=0.04).

Whilst not studying resistant organisms per se, but relevant in understanding durations of treatment and how they may affect colonisation patterns, Dennesen et al[99] studied 27 patients treated for ventilator-acquired pneumonia, who had an endotracheal aspirate taken for culture

every 3 days. They showed that new acquisition of colonisation by *P. aeruginosa, Staphyloccocus aureus* and *Enterobacteriaceae* species increased steadily by day, being rare at day 3 and more common by day 6, and increasing to day 15 (the end of their follow up). The authors suggested, based on previous work, that this represented selection for indigenous strains with higher levels of resistance due to antibiotic selection pressure. They concluded that in patients with good clinical improvement by 6 days, prolonging antibiotic therapy to or beyond 14 days resulted in no improvement in outcome, but an increase in colonisation with new (and potentially resistant) organisms.

In terms of evidence in other settings, which I have extended to studies in children due to the lack of studies overall, Ruhe et al[100] studied 303 patients with *S. pneumoniae* bacteraemia, of which 90 (32%) were due to penicillin-nonsusceptible isolates; patients with non-susceptible isolates had significantly longer prior exposure to beta-lactam antibiotics compared to those with susceptible isolates (15 vs 10 days, p=0.001). The Odds Ratio(OR) of beta-lactam exposure in the prior 6 months for patients with penicillin-nonsusceptible isolates was 6.44 (95% CI 3.80-10.94 p<0.001).

Schrag et al[101] randomised 795 children with respiratory tract infections to receive amoxicillin at either 90mg/kg for 5 days or 40mg/kg for 10 days, and studied penicillin nonsusceptibility of *S. pneumoniae* in nasopharyngeal specimens. They found that the risk of subsequent 28-day carriage of non-susceptible isolates was significantly lower in the short course group (24% vs 32%, Relative Risk (RR) 0.77, 95% CI 0.60-0.97 p=0.03).

Hillier et al[102] conducted a case-control study of 903 patients with *E. coli* urinary tract infections, with cases being patients with ampicillin or trimethoprim resistant infections and controls with ampicillin and trimethoprim susceptible infections. They found that the most recent amoxicillin prescription being 7 days or longer was associated with ampicillin

resistance (OR 3.91 95% CI 1.64-9.34), but that there was no association with prescriptions of less than 7 days (OR 1.79, 95% CI 0.65-2.19) a lower dose prior prescription was also associated with higher risk of resistance (OR 2.07, 95% CI 1.39-3.06), whilst high dose prescription was not (OR 0.91, 95% CI 0.49-1.70) . Similar results for duration were seen with trimethoprim resistance.

Hay et al[103] studied the *E. coli* isolates grown from urine of 2943 asymptomatic adult patients attending primary care for a non-infection-related reason. Of the 618 patients with available microbiological and prescribing data, they found a dose-dependent effect, with a 1% increase in odds of resistance to either trimethoprim or amoxicillin for every trimethoprim tablet prescribed previously (adjusted OR 1.01, 95% CI 1.01-1.02, p =0.001).

Guillemot et al[104] studied *S. pneumoniae* isolates from pharyngeal samples of 941 children, finding that prior beta-lactam treatment of more than 5 days was associated with increased risk of penicillin non-susceptible versus susceptible isolates (adjusted OR=3.9, 95% CI 1.4-11.2, p=0.02), whilst treatment <5 days was not associated (p=0.9) . However, it must be noted that there were both far smaller numbers of individuals receiving the shorter duration, reducing power, and no non-susceptible isolates in this group (6/138 isolates were non-susceptible in the long treatment group, 0/23 isolates were non-susceptible in the short treatment group) hence they were unable to calculate OR or 95% CIs for shorter duration therapy.

Nasrin et al[105] studied pneumococcal isolates from nasal swabs in 451 children, and found that there was no evidence of association between penicillin-resistance and prior antibiotic exposure of 1-7 days (7/64 individuals with exposure carried non-susceptible isolates 11%, OR 0.86, 95% CI 0.37-2.02 p=0.73), or 8-14 days (13/74 18%, OR 1.50, 95% CI 0.73-3.06, p=0.27), but an association existed for exposure >14 days (16/61 26%, OR 2.5, 95% CI 1.30-

4.86, p=0.006). They estimated the modelled odds of penicillin-resistant isolate carriage to be 4% higher for each additional day of beta-lactam antibiotics in the six months prior to sample collection.

Finally, it is worth noting that in the Costelloe et al[64] meta-analysis of prior antibiotic exposure and risk of resistant infection, longer courses were associated with higher rates of resistance.

In summary, for the majority of infections seen in general medicine, shorter courses appear to be as effective as longer courses, and it is reasonable, based on some limited evidence from studies, to consider that longer courses are more associated with resistant infection that shorter courses.

1.3.6 **Altering dose and effects on resistance**

1.3.6.1 ***High dose or low dose?***

The dose of antibiotics used is rarely mentioned in public health literature as a method of reducing development of antimicrobial resistance, despite this being the focus of Alexander Fleming's famous speech[89]. One issue with encouraging higher doses is that in terms of metrics, it does not fit easily with the drive to reduce antibiotic consumption, commonly measured in national and international monitoring in Defined Daily Doses (DDDs) which convert mgs taken of each antibiotic into what would be a "standard" dose for that antibiotic, enabling sensible comparisons between antibiotics. However, higher doses will lead to an apparent increase in consumption.

1.3.6.2 ***Evidence for use of higher doses and resistance selection***

There is some evidence that lower doses may be more selective for resistance than higher doses. The concept of a concentration 'selection window' had previously been proposed by

Baquero et al[106], whereby there was a concentration of antibiotic which was ineffective and produced little or no selective effects, and a concentration that killed effectively, and a 'window' in-between, which allowed growth of the less susceptible strains, and their subsequent progression, through further mutation, to full resistance. Beta-lactam, fluoroquinolone and aminoglycoside under-dosing have been shown to enhance selection for resistance at physiological concentrations in in-vitro studies[107,108,109].

The other reason that lower dose may be selective for resistance in vivo is that, due to excretion of antibiotics, intermittent dosing will lead to variable serum levels, especially for antibiotics with shorter half-lives. The lower the dose, potentially the shorter the duration of inhibition, and the longer the duration of non-inhibition, during which time the more resistant bacteria are able to multiply, and induce enzymes or transporter mechanisms to increase resistance, and more resistant mutants are selected for. The more resistant strains with higher MICs will also spend comparatively shorter times at inhibitory concentrations compared to lower MIC strains, giving them a significant survival advantage (**Figure 5**). For beta-lactams with relatively short half-lives, it has been suggested that extended or continuous infusion may assist in maximising the amount of time spent at inhibitory concentrations[110], but there have been only two studies which have looked at resistance selection with continuous vs intermittent infusions, and both did not compare the same antibiotic given intermittently or continuously[111,112].

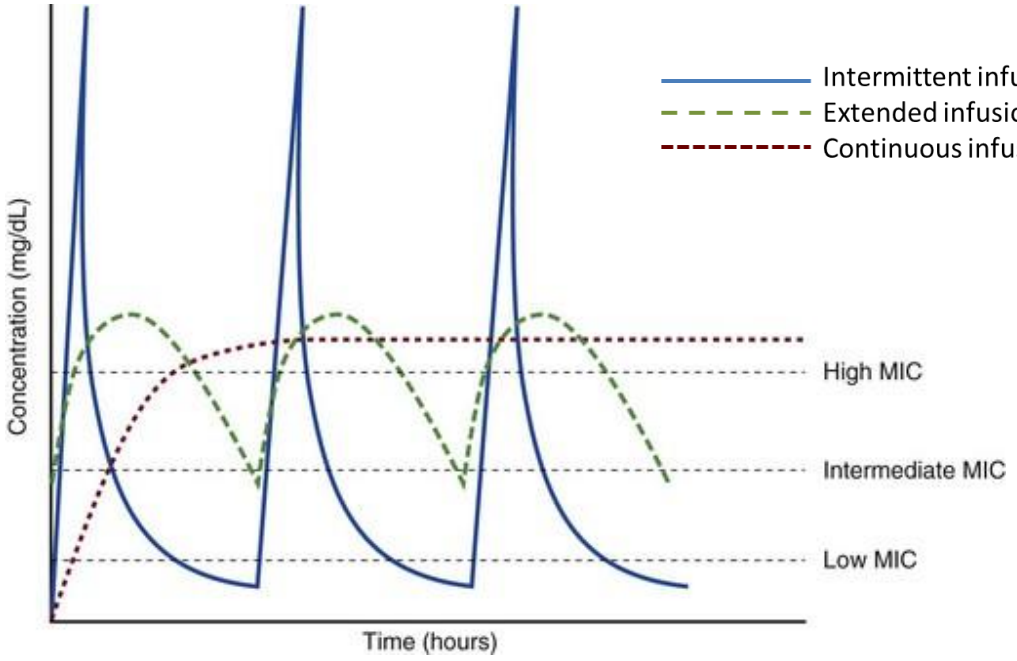


Figure 5: Impact of increasing Minimum Inhibitory Concentration (MIC) on time spent at inhibitory concentrations, with intermittent, extended and continuous infusions, adapted from Czonowski et al[110]

There are relatively few clinical studies that have assessed associations between dosing and resistance. In Guillemot study[104] of *S. pneumoniae* carriage in children. Among *S. pneumoniae* carriers, a prior beta-lactam low daily dose was associated with an increased risk of penicillin-resistant *S. pneumoniae* carriage. 6/84 exposed to low dose beta-lactams were penicillin –nonsusceptible carriers , adjusted OR 7.5, 95% CI 2.5-22.8 p<0.0. Conversely 0/54 individuals exposed to high dose beta-lactams were penicillin –nonsusceptible carriers (OR/95% CI not calculated, p=0.9).

. The Schrag[101] study, which compared short course, high dose amoxicillin with standard dose and length, found that, of pneumococcal carriers, children from the high dose group had a lower MIC and lower risk of carrying resistant *S. pneumoniae.* 24/355(7%) individuals in short/high dose group were penicillin non-susceptible carriers vs 32/346 (9%) individuals in

the standard therapy group by day 28. In a between- group comparison, the simple RR of penicillin-nonsusceptible isolate carriage in short high dose vs standard group low dose was 0.77, (95% CI 0.60-0.97 0=0.03), with the conditional RR of penicillin-nonsusceptible isolate carriage was 0.78 (95% CI 0.65-0.95 p=0.01) (evaluating the risk conditional on pneumococcal carriage).

Whilst there are not currently any defined initiatives in the UK to encourage use of higher doses of beta-lactams to address resistance, it is notable that in my clinical career, there has been a widespread discontinuation of the use of 250mg amoxicillin courses that were occasionally used during my medical school years circa 2003, and the recommended dose for oral treatment is now 500mg amoxicillin three times a day.

1.3.6.3 *Evidence for use of alternative dosing regimens and resistance*

An alternative method of addressing the issue of sub-therapeutic dosing encouraging resistance is to use alternative treatment regimens such as loading doses and continuous infusions, to reduce the time taken to attain therapeutic concentrations and maximise the percentage of time spent at these levels, together with regular assays of drug levels to ensure that concentrations do not reach toxic levels. The intensive care/high dependency environment is well set up to manage these regimens. Progress in medical device design, such as the use of elastomeric devices, and provision of services such as outpatient antibiotic therapy nurses and training for patients, are making these types of regimens more accessible to medical inpatients. A number of studies have shown improved clinical outcomes with continuous infusion[113], with meta-analyses generally finding that continuous infusion, especially in patients with severe sepsis[114], is associated with reduced hospital mortality. However no studies to date have demonstrated an effect of either loading doses or continuous infusions on future risk of resistant pathogens[115], though in-vitro and mathematical modelling strategies suggest that this may be effective[116].

1.3.7 **Spectrum - 'broad spectrum' vs narrow spectrum antibiotics**

There is no universally accepted definition of a broad spectrum antibiotic. The original definition of broad spectrum is an antibiotic which acts against both gram-positive and gram-negative bacteria, or acts against a wide range of bacteria. Some have even called for the term to be scrapped, viewing it as inherently unhelpful[117]. Recent UK financial incentives focused specifically on reducing piperacillin-tazobactam and carbapenem use[9], two of the "broadest" spectrum antibiotics, though these incentives have now been discontinued. Taking a different approach, the World Health Organisation released a classification of antibiotics in 2017, updated in July 2019[118], created by expert consensus and based on assessment of resistance potential, grouping antibiotics as Access (should be widely available and used), Watch (can be used but more sparingly), or Reserve (should be used as last resort)[119]. The 2019 Update specified a target for 60% of national consumption to be from the Access group antibiotics.

Despite many initiatives focusing on reducing broad spectrum antibiotic use, there are no studies or meta-analyses that I can find specifically comparing broad spectrum and narrow spectrum antibiotics as a group, in terms of impact on resistance selection. There are many studies that look at the effects of changing antibiotic policies to encourage less broad spectrum use, or less use of antibiotics perceived as 'high risk' for selection for either *Clostridium difficile* infection or Extended Spectrum Beta Lactamase producing Enterobacteriaceae (ESBLs), and these are summarised in a following section looking at antibiotic interventions.

1.3.8 **Other factors that may impact on resistance selection**

There are many other antibiotic characteristics that are increasingly being seen as important to overall resistance selection. Key to this is the increased understanding of the human body, and human health, as being dependent on the relationship between the body and its colonising micro-organisms - the microbiome. Antibiotics rarely work solely on the infecting pathogen: they will potentially affect any susceptible bacteria colonising the individual. There is increasing evidence that these colonising micro-organisms may often play a protective role in preventing pathogenic overgrowth and infection of bacterial strains, either by direct killing[120,121], immune stimulation[122], or competition for resources[123]. Antibiotic-mediated disruption of the protective colonising microbiome has been demonstrated to increase the ability of resistant organisms to colonise[124], and has been proposed as a major mechanism by which circulating resistant strains can establish colonisation, infection, and subsequently transmission.

The gut microbiome is particularly important, being the site of highest microbial density in the body, and indeed, almost anywhere in nature[125], and being a major site of colonisation with resistant bacteria, most notably with resistant Enterobacteriaceae. It is also the site of significant horizontal gene transfer[126]. Thus the metabolism of antibiotics, and overall ecological effect on the gut microbiota, is increasingly been seen as potentially having major impacts on the degree to which an antibiotic will select for resistant organism colonisation and carriage[127] (**Figure 6**).

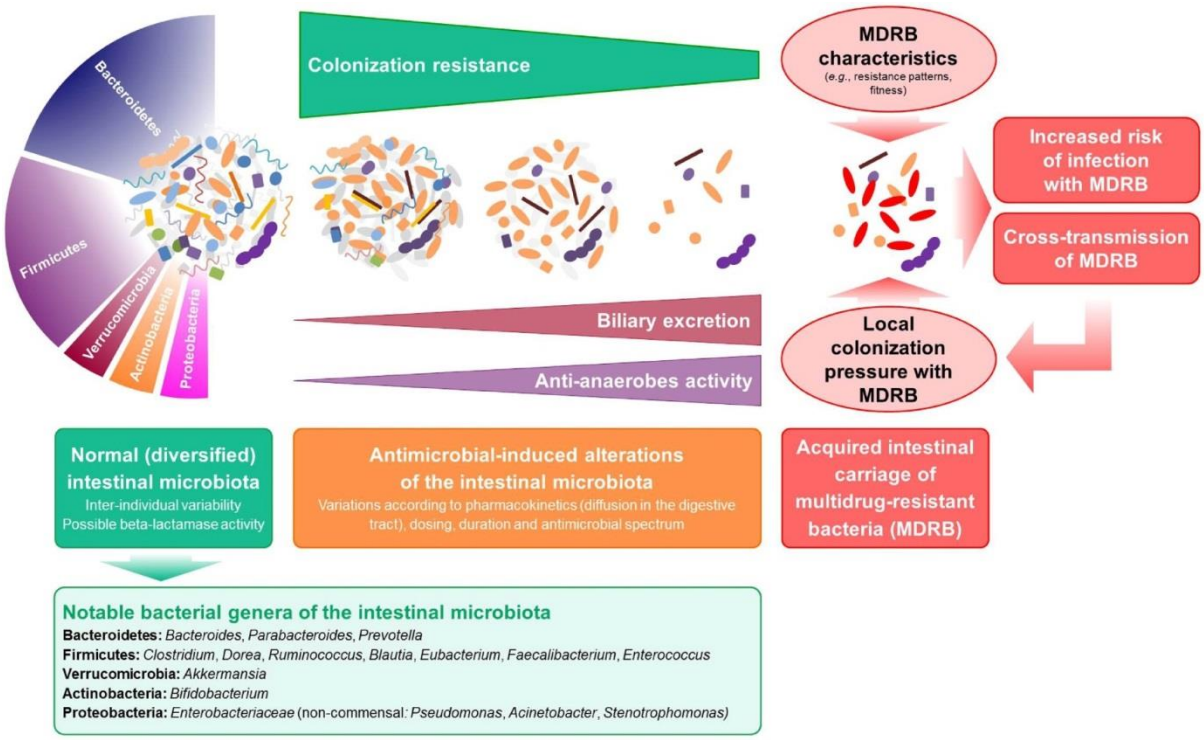


Figure 6: Factors that contribute to the colonisation and risk of infection from resistant bacteria that colonise the gut, from Woerther et al[123]

The route of administration may also play a role in resistance selection – in mouse models, oral antibiotics have been shown to have much larger effects both on the gut microbiota and on resistance selection compared to the same antibiotics delivered intravenously[128]. The individual pharmacokinetics of antibiotics may also come into play, such that antibiotics that are given intravenously and excreted renally may bypass the gut, whilst others that are excreted in active form via the biliary tree may have much larger selective effects for resistance in the gut microbiota.

Whilst there is value to the simplistic model of resistance being proportional to overall exposure to antibiotics, the combination of all these factors suggest that the 'resistance potential', or the in-vivo selective effect of antibiotics is likely to be far from straightforward.

As such, the need for studies that assess the resistance-selective effects in vivo, in real-life hospital settings are needed. Identifying antibiotics with the most or least resistance-selective effects would be of great assistance to the clinician in identifying strategies to minimize resistance selection. It may be that particular antibiotics may cause much larger effects on resistance selection that their bacteriostatic/bacteriocidal spectrum first suggests, and conversely other antibiotics may cause very little resistance selection in vivo.

1.3.9 **Interventions to change antibiotic use and their effects on resistance**

The Infectious Diseases Society of America (IDSA) defines antibiotic stewardship as "co-ordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration." Initiatives to change antimicrobial use in hospitals largely fall under the umbrella of Antibiotic Stewardship, where a wide range of interventions are used, including implementation or change of guidelines, restrictions on the use of particular antibiotics, and measures to change the duration of prescribing or reduce perceived 'inappropriate' use.

There are now numerous studies published which report the effects of such stewardship activities. The most recent systematic review of interventions to improve antibiotic prescribing for hospital inpatients by Davey et al included 221 studies, mainly from North America and Europe. They found that stewardship initiatives can increase compliance with guidelines, reduce antibiotic treatment duration, and did not appear to increase risk of death. They concluded that antibiotic stewardship interventions probably reduced length of stay[68]. However, they highlighted the lack of studies that reported impact on resistance, and noted that even in studies where microbiological outcomes were reported, overall there were too

few studies, too much variance in outcomes, and too low event rates, to reliably assess the effects of changes in antibiotic use on microbial outcomes.

There were 26 studies with sufficient data on prescribing and microbiological outcomes included. I will briefly review these studies, and consider what conclusions I can draw from them (summary of studies in **Table 1**). Four studies only measured *C. difficile* infection as a microbiological outcome (i.e. considered a separate infection); whilst technically this is not a resistance outcome, they add some value in their insights.

1.3.10 **Antibiotic interventions, and their effect on prescribing and resistance**

Aldeyab et al[129] studied the effect of a change in guidelines in hospital and the community, minimising use of 'high risk' antibiotics, and describing antibiotics as 'medium risk' and 'low risk' antibiotics at four related UK secondary care centres,. In January 2008 antibiotic policy was changed in primary care and hospital formularies. In hospital the intervention included restrictions on non-formulary antimicrobials requiring consultant microbiologist approval and audit and feedback. In a time series analysis covering January 2006-June 2010, the intervention was associated with a significant decrease in overall use of 'high risk' antibiotics, with no change in overall use of 'medium risk' and 'low risk' antibiotics. There was no significant change in MRSA incidence, but there was a significant reduction in the overall trend in MRSA incidence in the hospital and community.

Ananda-Rajah et al[130] studied the effect of a number of interventions on an Australian intensive care unit. Electronic decision support systems were introduced January 2001, with ID service ward rounds in 2004, and full time infection control practitioners appointed November 2004 to oversee outbreak measures including isolation and contact precautions,

together with change in hand hygiene procedures. In a time series analysis, there was a significant decrease in fluroquinolone, cephalosporin, aminoglycoside, glycopeptide and macrolide prescribing, and overall broad spectrum antibiotic consumption (with change point September 2004), and a significant increase in antipseudomonal penicillin consumption. There was a significant decrease in MRSA bacteraemia rates and trend with change point January 2004.

Buising et al[131] conducted a time-series analysis of the effect of introducing electronic prescribing and restrictions in 2005 in a tertiary care centre in Australia 2000-2010. Targeted antibiotics required Infectious Diseases clinician authorisation (notably azithromycin, aztreonam, 3rd and 4th generation cephalosporins, quinolones, carbapenems, colistin, gentamicin, piperacillin/tazobactam, teicoplanin and vancomycin). There was a reduction in prescribing of 3rd and 4th generation cephalosporins, and a reduction in the trend in prescribing of carbapenems, quinolones and aminoglycosides, with a corresponding increase in extended-spectrum penicillin prescribing. They studied microbial outcomes in all patients with a positive blood culture 2003-2006 (two years before and after the intervention) and found a trend towards increasing susceptibility of *Pseudomonas* spp. isolates to carbapenems and aminoglycosides, a trend towards increasing susceptibility of *S. aureus* to methicillin, and an increase in the susceptibility of *E. coli* isolates susceptible to cefazolin. They found no evidence of change in 30 day mortality or length of stay in patients with gram-negative bacteraemias.

Chan et al[132] studied the effect of implementing a computerised prescribing service in a tertiary centre in Taiwan. In 2004 they implemented the computerised system, together with an automated prompt to ID physicians to review and electronically provide feedback/advice for any prescription of 'restricted' antibiotics (3rd/4th generation cephalosporins, aminoglycosides, carbapenems, monobactams, extended-spectrum penicillins,

fluoroquinolones and glycopeptides). They studied antimicrobial consumption 2003-2009. They found small but significant decreases in gradient of consumption for 3rd and 4th generation cephalosporins, fluoroquinolones and glycopeptide, and an large increase in carbapenem trends. MRSA rates continued a declining trend, an increasing trend of ESBL *E. coli* and *K. pneumoniae* rates continued during the study period, and there was no effect on *C. difficile* rates. Increases in carbapenem prescribing were attributed to increases in ESBL rates.

A study by Cook et al[133], studied the effect of implementing a review of all broad-spectrum antimicrobial prescriptions at a US tertiary care centre in 2001. Quarterly antimicrobial consumption was reviewed 1999-2003. Compared to the six quarters before institution of the reviews, there was a decrease in broad-spectrum use and overall antimicrobial use. Susceptibilities of common nosocomial gram-negative organisms did not change significantly over the 3 years of the programme. The MRSA rates increased significantly in non-intensive care areas, and decrease significantly in intensive care areas, which the authors hypothesised may have been due to infection control measures implemented during the study period.

In a 2nd study, Cook et al[133] conducted a retrospective time-series analysis of antimicrobial use and microbial isolates in a US tertiary care centre over 2000-2009, and studied the effect of adding ertapenem (a carbapenem without *P. aeruginosa* activity) to the hospital formulary in 2002. They found that, following introduction, there was a reduction in ciprofloxacin prescribing, and a reduction in the percentage of *P. aeruginosa* isolates resistant to carbapenems, but no change in the susceptibility patterns of Enterobacteriaceae or *Acinetobacter baumanii*. They speculated that cross-resistance may have played a role, with reduced quinolone use leading to less induction of efflux pumps in *P. aeruginosa*, which led to less carbapenem resistance.

In a third study by Cook et al[134], they studied the effect of implementing an electronic prescribing and medical records system in a US tertiary care centre in July 2007. They studied antimicrobial consumption 2005-2009 and found that compared to the 10 quarters prior to implementing the electronic system, there was a 28.8% decrease in overall consumption of the 41 most commonly used antibacterial agents. There was a significant decrease in consumption of extended spectrum penicillins, cephalosporins, quinolones, clindamycin, macrolides, vancomycin and metronidazole. There was a significant increase in consumption of carbapenems. There was a significant decrease in Nosocomial C. difficile infection decreased and nosocomial MRSA infections decreased by following implementation. They assessed the correlation between antibiotic classes and infection, and found the highest correlation with MRSA rates was with quinolone use, whilst for C. difficile the highest correlation was with cephalosporin use.

Dancer et al[135] conducted a retrospective analysis of the effect of restriction of use of cephalosporins and quinolones in a UK secondary care centre. Consumption of antibiotics was analysed from November 2007 to November 2009, with the intervention starting January 2008. They found a reduction in average monthly consumption of ceftriaxone and ciprofloxacin. They saw a decrease in hospital acquisition rates for MRSA and ESBL infections in the last six months of the study compared to the first six months, but it did not reach significance and neither did any change in trends. *C. difficile* cases were already decreasing prior to the intervention period and there was no significant change in rates or trends.

Fowler et al[136] studied the effect of a restrictive antibiotic policy on three medical wards at a UK teaching hospital. In July 2001 a narrow spectrum antibiotic policy was implemented. Using a segmented regression analysis January 2001-March 2003, they saw a significant reduction in amount of and trend in amoxicillin/clavulanic acid and cephalosporin

consumption, a significant increase in amoxicillin consumption and a significant increase in the trend in benzylpenicillin consumption. Using a Poisson regression, they found a significant fall in *C. difficile* infection associated with the intervention, but no change in MRSA level or trend, and no significant effect on mortality.

Goldstein et al[137] also studied the effect of addition of ertapenem in September 2002 to a US secondary care centre, conducting a retrospective time series analysis of prescribing January 2002-December 2005, and the susceptibility of isolates from the hospital microbiology laboratory. There was a significant increase in ertapenem prescribing, significant decrease in imipenem prescribing and no significant change in levofloxacin, cefoxitin, piperacillin-tazobactam and cefepime prescribing. Susceptibility of *P. aeruginosa* isolates to imipenem and cefepime increased. Conversely *E. coli* susceptibility to levofloxacin decreased, with no other significant changes to susceptibilities in this organism, *Klebsiella* spp. or *Enterobacter cloacae*.

Grohs et al[138] studied the effect of a change in antibiotic formulary, replacing ceftriaxone with cefotaxime in a French tertiary care centre in 2005. Studying antimicrobial consumption 2001-2012, they saw a significant increase in cefotaxime consumption and trends and significant decrease in ceftriaxone consumption and trends post intervention. At the start of the study period, there was an increasing incidence of Enterobacteriaceae harbouring high-level AmpC beta-lactamase (HL-CASE), (beta-lactamase resistant Enterobacteriaceae due to a particular molecular mechanism). In the post intervention period, there was a reduction in trend and stabilisation of the incidence of HL-CASE incidence, especially *for Enterobacter cloacae*. This was theorised to be due to selection of resistant isolates in the digestive tract[139], due to biliary excretion of ceftriaxone in active form (which is not a feature of cefotaxime).

Kim et al[140] studied the effect of restricting use of 3rd generation cephalosporins in November 2004 in 750-bed Korean Hospital. Volume of antibiotic use and susceptibility patterns of all isolates was assessed February 2004-April 2006. They showed a non-sustained decrease in 3rd generation cephalosporin prescribing with parallel increases in 2nd generation cephalosporin, quinolone and piperacillin/tazobactam prescribing. The proportion of *K. pneumoniae* isolates that were ESBLs increased during the pre-intervention and early intervention periods, and fell during the post-intervention period. The proportion of imipenem-resistant *P. aeruginosa* isolates increased then declined significantly in the post intervention period. The proportion of imipenem/piperacillin-tazobactam-resistant *A. baumanii* did not initially change, but declined significantly in the post intervention period. There was no change in ESBL-producing *E.coli*.

Knudsen et al[141] studied the effect of multiple interventions including cephalosporin, fluoroquinolone and carbapenem restriction at a Danish tertiary care centre in 2010. There were educational sessions, guideline changes and distribution, enhanced infection control measures and printed feedback. A time series analysis of prescribing and microbiological data 2008-2012 showed a pronounced and significant reduction in cefuroxime prescribing, with smaller increases in ertapenem, piperacillin-tazobactam and beta-lactamase susceptible penicillin prescribing, and no change in quinolone, meropenem, co-amoxiclav and macrolide prescribing. They found a reduction in proportion of *K. pneumoniae* isolates which were ESBL producers and a reduction in the incidence of ESBL *K. pneumoniae* infections, but no significant effect on ESBL *E. coli* infections. Faecal carriage in surveillance wards of ESBL strains decreased significantly. There was no effect seen on mortality.

Lafaurie et al[142] analysed the effect of a set of multifaceted interventions to reduce fluoroquinolone use at a tertiary hospital January 2000-March 2010. Following implementation of audit and feedback, written guideline changes and daily antibiotic

counselling for all patients with positive microbiological cultures introduced between September 2005-March 2006, fluoroquinolone prescribing was reduced. In a segmented regression model, they found a reduction in the trend in resistance rates in *P. aeruginosa*, and a reduction in the rates of resistance for *S. aureus* to methicillin with no significant change in trend.

Lautenbach et al[143] studied the effect of a change in antibiotic policy implemented between 1994-1998 at a US quaternary care centre, restricting the use of vancomycin and 3rd generation cephalosporins. They studied antimicrobial consumption and Vancomycin Resistant Enterococci (VRE) prevalence between 1991 and 2000. They found a significant initial decrease in vancomycin use which returned to pre-intervention levels by the end of the study period. They found a significant decrease in 3rd generation cephalosporin use. They found a steady increase in VRE presence with little impact of the change in antibiotic policy on prevalence.

Lee et al[144] studied the effect of extended-spectrum cephalosporin restriction in 2002 in a Korean paediatric tertiary care centre, with a change in guidance and recommendations by the infectious diseases team to discourage use of these drugs and encourage use of penicillins. Isolates from normally sterile sites and ward antibiotic consumption data were analysed January 1999-December 2005. There was a significant increase in piperacillin-tazobactam use, a significant decrease in extended-spectrum cephalosporin use, and no significant effect on prescribing of ampicillin/sulbactam, carbapenems and cephamycins. There was a significant decrease in the prevalence of ESBL strains, driven mainly by a reduction in ESBL *K. pneumoniae*. Surprisingly there was a significant increase in susceptibility to piperacillin-tazobactam in *E. coli* isolates, which the authors offered no obvious explanation. There was no significant change in *A. baumanii*, *Enterobacter* spp. and *P.aeruginosa* resistance patterns.

Liebowitz et al[145] studied the effect of an education intervention in July 2005 aimed at reducing the prescribing of intravenous ciprofloxacin and 3rd generation cephalosporins at a UK tertiary care centre. They saw a significant decrease in ciprofloxacin and 3rd generation cephalosporin dispensing in the 18 months post intervention compared to 18 months prior to the intervention. They found a significant reduction in overall rate of MRSA bacteraemia cases, with no change in trend. Before the intervention, MRSA colonisation rates were decreasing, and this continued after the intervention, with no significant change in trend.

May et al[146] studied the effect of a change in the antibiotic formulary in the trauma/burns intensive care unit of a US tertiary care centre in 1998. This change aimed to minimise cephalosporin use and introduced piperacillin/tazobactam. They found a significant reduction in 3rd generation cephalosporin and total cephalosporin use, and a significant increase in piperacillin/tazobactam prescribing in the 5 quarters after intervention compared to the 3 quarters before the intervention. They saw a significant decrease in VRE infections. In the other intensive care units of the hospital, which did not have a change in formulary or cephalosporin use, there was no reduction in VRE seen.

Meyer et al[147] studied the effect of restricting cephalosporin use on a German intensive care unit. In July 2004, there was a guideline change with 3rd generation cephalosporins being substituted with piperacillin-tazobactam for treatment of peritonitis, and recommendations for open fracture treatment were changed from 5-7 days to a single dose preoperatively. In a time series analysis covering 30 months before and after the intervention there was a significant reduction in 3rd generation cephalosporin prescribing, and a significant increase in piperacillin/tazobactam prescribing. There was a reduction in the percentage of *K. pneumoniae* isolates resistant to 3rd generation cephalosporins and (surprisingly) *K. pneumoniae* resistant to piperacillin, but an increase in the number of piperacillin-resistant *E. coli* infections and ampicillin/sulbactam resistant *E. coli* infections per 1000 patient bed-days.

Petrikkos et al[148] studied the effect of a change in antibiotic formulary replacing broad-spectrum cephalosporins with piperacillin/tazobactam as first line empirical therapy in a Greek tertiary care centre in . They found a significant decrease in ceftazidime consumption, but not change in consumption of other 3rd generation cephalosporins, and a significant increase in piperacillin/tazobactam prescribing. They saw a significant decrease in resistance to 3rd generation cephalosporins in *K. pneumoniae* isolates, and an overall reduction in the incidence of ESBL-producing isolates. They saw no change to resistance to piperacillin/tazobactam in *K. pneumoniae*. There was no significant effect seen on resistance patterns in *E. coli*.

Tangden et al[149] studied the effect of guideline changes and an educational intervention to reduce the use of fluoroquinolones, carbapenems and 2nd and 3rd generation cephalosporins in a Finnish tertiary care centre in October 2006 together with enhanced infection control measures. In a time series analysis January 2000-December 2007, they saw a significant reduction in amount of and trends in cephalosporin consumption, no change in trends in fluoroquinolone and carbapenem prescribing with increasing overall carbapenem use, and a significant increase in piperacillin/tazobactam overall use and trend. An ESBL outbreak ongoing since 2005 terminated in January 2007. There was no change in rates of resistance to tested antibiotics in *E. coli*, *K. pneumoniae* or *P. aeruginosa* in blood isolates July 2005-June 2009.

Willemsen et al [150] conducted an analysis of prescribing January 2006-December 2007, and resistance data January 2004-December 2007 at a Dutch tertiary care centre. To try and reduce quinolone prescribing, in May 2006, new guidelines were issued, followed in November 2006 with an advisory note against ciprofloxacin use for urinary tract infections, and in January 2007, active monitoring and feedback of prescribing. They found a reduction

in overall quinolone use, with a reduction in trend of quinolone resistance rates in *E. coli* isolates, and no other significant changes to resistance patterns.

Four studies focused on *C. difficile* infection alone as an outcome.

Jump et al[151] studied the effect of implementing an on-site infectious diseases service to a US long term care facility affiliated with a tertiary care centre from July 2009 onwards. Patients with possible infection were referred to the service (of which over half were already receiving antibiotics), and antibiotic recommendations given. They studied antibiotic administration in the 36 months before and 18 months after the introduction of the service, and saw a significant decrease in overall antibiotic administration, and tetracycline, clindamycin, co-trimoxazole, beta-lactam/beta-lactamase combination, and fluoroquinolone administration and trends. They found a significant reduction in the rate of positive C. difficile tests in the post-intervention phase compared to the pre-intervention phase.

McNulty et al[152] studied the effect of introducing a restrictive antibiotic policy in 1994, prioritising use of antibiotics that had less effect on gut bacteria, in a UK tertiary care centre elderly care ward, particularly considering impact on *C. difficile* infection and clinical outcomes. In July 1994 the antibiotic policy changed from an encouragement to use narrow spectrum antimicrobials to recommendations for either IV benzylpenicillin, IV trimethoprim and/or a single dose of gentamicin. Additional infection control measures were also initiated. There was a significant reduction in cefuroxime use, the number of *C. difficile* infections in the 7 months after the policy was initiated was significantly less than the number in the 7 months before, and there was no difference in clinical outcome.

Talpaert et al[153] studied the effect of a change in antibiotic policy in April 2006, prioritising 'low *C. difficile* risk' antibiotics in a UK tertiary care centre. Additionally all 'high risk' antibiotic prescriptions for inpatients were reviewed by an antibiotic management team. In a

time series analysis covering 12 months before and after guideline change, there was a significant decrease in fluoroquinolone and cephalosporin consumption, and no change in clindamycin, amoxicillin or co-amoxiclav use. Modelling *C. difficile* using negative binomial regression, there was a significant decrease in *C. difficile* infection associated with the intervention.

Valiquette et al[154] studied the effect of a series of interventions in a Canadian secondary/tertiary care centre. Prior to antibiotic change, infection control procedures were implemented September 2003 (isolation, disposable equipment, terminal disinfection) with no effect on *C. difficile* incidence. In October 2004 a change in antibiotic guidance aimed to reduce targeted high risk antibiotics and durations of treatment, and was implemented together with ward-based feedback. In a time series analysis covering January 2003-April 2006, there was a significant reduction in cephalosporin, clindamycin, macrolide and ciprofloxacin consumption, a significant increase in moxifloxacin and piperacillin/tazobactam use, and a significant reduction in *C. difficile* infection incidence. There was also a reduction in the trends in *C. difficile* infection incidence following guideline changes.

Table 1: Summary of 14 antibiotic intervention studies that reported on resistance or microbiological outcomes, and other clinical outcomes

Study	Intervention	Effect on prescribing	Effect on resistance
Studies with resistant infection and/or colonisation as an outcome			
Aldeyab et al[129]	**Study design**: Interrupted Time Series **Timeframe**: 2006- 2010 **Intervention**: 2008 Change in guidelines, reducing 'high risk' antibiotics in hospital and community including restrictions and feedback sessions	Significant decrease in overall use of 'high risk' antibiotics, with no change in overall use of 'medium risk' and 'low risk' antibiotics	No significant change in MRSA incidence, but there was a significant reduction in the overall trend in MRSA incidence in hospital and community
Ananda-Rajah et al[130]	**Study design**: Interrupted Time Series **Timeframe:** a 2000-2008 **Interventions:** 2001,2004 Increased infectious diseases advice, and enhanced infection control measures	Significant decrease in fluroquinolone, cephalosporin, aminoglycoside, glycopeptide and macrolide prescribing, and overall broad spectrum antibiotic consumption, significant increase in antipseudomonal penicillin consumption	Significant decrease in MRSA bacteraemia rates
Buising et al [131]	**Study design**: Interrupted Time Series **Timeframe:** a 2000-2010 **Intervention:** 2005 Targeted antibiotics required infection diseases clinician approval	Reduction in prescribing of 3rd and 4th generation cephalosporins, reduction in upwards trend of prescribing of carbapenems, quinolones and aminoglycosides, increase in extended-spectrum penicillin prescribing	Reduction in resistance of *Pseudomonas* spp. isolates to carbapenems and aminoglycosides, trend towards increasing susceptibility of *S. aureus* to methicillin, and an increase in the susceptibility of *E. coli* isolates to cefazolin
Chan et al[132]	**Study design**: Interrupted Time Series	small but significant decreases in gradient of consumption for 3rd and 4th generation	No changes in trends in MRSA, *C.difficile* or ESBL trends. MRSA rates continued a declining

Study	Intervention	Effect on prescribing	Effect on resistance
	Timeframe: 2003-2009 **Intervention:** 2004 Computerised prescribing service, ID physician electronic feedback/advice for restricted' antibiotics	cephalosporins, fluoroquinolones and glycopeptide, and an large increase in carbapenem trends.	trend, an increasing trend of ESBL *E. coli* and *K. pneumoniae* rates and *C. difficile* rates continued
Cook et al[133]	**Study design**: Interrupted Time Series **Timeframe:** 1999-2003 **Intervention:** 2001 Review of all broad-spectrum antimicrobial prescriptions.	decrease in broad-spectrum use and overall antimicrobial use.	No change in susceptibilities of common nosocomial gram negative organisms. Increase in MRSA rates during study period.
Cook et al[155]	**Study design**: Interrupted Time Series **Timeframe:** 2000-2009 **Intervention:** 2002 Jan 2002: addition of ertapenem to hospital formulary	Reduction in ciprofloxacin prescribing	Reduction in resistance in *P. aeruginosa* to carbapenems, no effect on resistance in Enterobacteriaceae and *A. baumanii*
Cook et al[134]	**Study design**: Interrupted Time Series **Timeframe:** 2005-2009 **Intervention:** 2007 Implementation of electronic prescribing and medical records system	decrease in overall consumption of the 41 most commonly used antibacterial agents significant decrease in consumption of extended spectrum penicillins, cephalosporins, quinolones, clindamycin, macrolides, vancomycin and metronidazole. significant increase in consumption of carbapenems	Significant decrease in nosocomial *C. difficile* infection and nosocomial MRSA infections
Dancer et al[135]	**Study design**: Interrupted Time Series **Timeframe:** a 2007-2009 **Intervention:** 2008	Reduction in average monthly consumption of ceftriaxone and ciprofloxacin	No significant changes in MRSA, ESBL or *C. difficile* trends

Study	Intervention	Effect on prescribing	Effect on resistance
	Cephalosporin and quinolone restriction January 2008		
Fowler et al[136]	**Study design**: Interrupted Time Series **Timeframe:** 2001-2003 **Intervention:** 2001 Restrictive antibiotic policy	Significant reduction in amount and trend in amoxicillin/clavulanic acid & cephalosporin consumption, significant increase in amoxicillin consumption, significant increase in benzylpenicillin trend	Significant fall in *C. difficile* infection associated with the intervention, but no change in MRSA level or trend
Goldstein et al[137]	**Study design**: Interrupted Time Series **Timeframe:** 2002-2005 **Intervention:** 2002 Addition of ertapenem and substitution of ampicillin-sulbactam for ertapenem in hospital formulary	Reduction in imipenem prescribing, no change in levofloxacin, cefoxitin, piperacillin-tazobactam and cefepime	Reduction in resistance of *P. aeruginosa* to imipenem and cefepime. Decreased susceptibility of *E. coli* to levofloxacin, no changes to *Klebsiella* spp. or *Enterobacter cloacae*
Grohs et al[138]	**Study design**: Interrupted Time Series **Timeframe:** 2001-2012 **Intervention:** 2005 Change in antibiotic formulary replacing ceftriaxone with	significant increase in cefotaxime consumption and trends and significant decrease in ceftriaxone consumption	Reduction in trends of Enterobacteriaceae harbouring high-level AmpC beta-lactamase (HL-CASE) and stabilisation in incidence especially *for Enterobacter cloacae.*
Lafaurie et al[142]	**Study design**: Comparative Interrupted Time Series **Timeframe:** 2000-2010 **Intervention:** 2005-2006 Audit and feedback, written guideline changes and antibiotic counselling for all patients with positive microbiological cultures	Fluoroquinolone prescribing reduced	Reduction in upwards trend in resistance rates in *P. aeruginosa*, reduction in rate of resistance for *S. aureus* to methicillin with no significant change in trend

Study	Intervention	Effect on prescribing	Effect on resistance
Lautenbach et al[143]	**Study design**: Interrupted Time Series **Timeframe:** 1991-2000 **Intervention:** 1994-1998 Change in antibiotic policy implemented, restricting the use of vancomycin and 3rd generation cephalosporins.	Significant initial decrease in vancomycin use which returned to pre-intervention levels by the end of the study period. decrease in 3rd generation cephalosporin use	Steady increase in VRE presence with little impact of the change in antibiotic policy on prevalence
Liebowitz et al[145]	**Study design**: Interrupted Time Series **Timeframe:** 2003-2007 **Intervention:** 2005 Educational intervention aimed at reducing the prescribing of intravenous ciprofloxacin and 3rd generation	Significant decrease in ciprofloxacin and 3rd generation cephalosporin dispensing	Significant reduction in overall rate of MRSA bacteraemia cases, with no change in trend. Before the intervention, MRSA colonisation rates were decreasing, and this continued after the intervention, with no significant change in trend.
Kim et al[140]	**Study design**: Interrupted Time Series **Timeframe:** 2004-2006 **Intervention:** 2004 Restriction of 3rd generation cephalosporins	Non-sustained decrease in 3rd generation cephalosporin prescribing with increase in 2nd generation cephalosporin, quinolone and piperacillin/tazobactam prescribing	Proportion of *K. pneumoniae* isolates which were ESBL producers increased during the pre-intervention and early intervention periods, and fell during the post-intervention period. The proportion of imipenem-resistant *P. aeruginosa* isolates increased then declined significantly post-intervention. The proportion of imipenem/piperacillin-tazobactam-resistant *A. baumanii* did not initially change, but declined significantly post-intervention. No significant change in ESBL-producing *E. coli*
Knudsen et al[141]	**Study design**: Comparative Interrupted Time Series **Timeframe:** 2008-2012 **Intervention:** 2010	Reduction in cefuroxime prescribing, with smaller increases in ertapenem, piperacillin-tazobactam and beta-lactamase susceptible penicillin	Reduction in proportion of *K. pneumoniae* isolates which were ESBL producers and a reduction in the incidence of ESBL *K. pneumoniae* infections. No significant effect on

Study	Intervention	Effect on prescribing	Effect on resistance
	Guideline change - cephalosporin, fluoroquinolone and carbapenem restriction	prescribing, with no change in quinolone, meropenem, co-amoxiclav and macrolide prescribing	ESBL *E. coli* infections. Faecal carriage in surveillance wards of ESBL strains decreased significantly
Lee et al[144]	**Study design**: Interrupted Time Series **Timeframe:** 1999-2005 **Intervention:** 2002 Extended-spectrum cephalosporin restriction	Significant increase in piperacillin-tazobactam use, a significant decrease in extended-spectrum cephalosporin use, and no significant effect on ampicillin/sulbactam, carbapenems and cephamycins	Significant decrease in the prevalence of ESBL strains, driven mainly by a reduction in ESBL *K. pneumoniae*. Significant increase in susceptibility to piperacillin-tazobactam in *E. coli* isolates. No significant change in *A. baumanii*, *Enterobacter* spp. and *P.aeruginosa* resistance patterns
May et al[146]	**Study design**: Interrupted Time Series **Timeframe:** 1995-1999 **Intervention:** 1998 Change in unit antibiotic formulary minimising cephalosporin use and introducing piperacillin/tazobactam	Significant reduction in 3rd generation cephalosporin and total cephalosporin use, and a significant increase in piperacillin/tazobactam prescribing	a Significant decrease in VRE infections
Meyer et al[147]	**Study design**: Interrupted Time Series **Timeframe:** 2002-2006 **Intervention:** 2004 Restriction of cephalosporin use	Significant reduction in 3rd generation cephalosporin prescribing, and significant increase in piperacillin/tazobactam prescribing	Reduction in the percentage of *K. pneumoniae* isolates resistant to 3rd generation cephalosporins and *K. pneumoniae* resistant to piperacillin, increase in the number of piperacillin-resistant *E. coli* infections and ampicillin/sulbactam resistant *E. coli* infections
Petrikkos et al[148]	**Study design**: Interrupted Time Series **Timeframe:** 2002-2004 **Intervention:** 2003 Change in antibiotic formulary replacing broad-spectrum cephalosporins with	Significant decrease in ceftazidime consumption, no change in consumption of other 3rd generation cephalosporins, significant increase in piperacillin/tazobactam prescribing.	Significant decrease in resistance to 3rd generation cephalosporins in *K. pneumoniae* isolates, reduction in the incidence of ESBL-producing isolates. No change to resistance to piperacillin/tazobactam in *K. pneumoniae*. No significant effect on resistance patterns in *E. coli*.

Study	Intervention	Effect on prescribing	Effect on resistance
	piperacillin/tazobactam		
Tangden et al[149]	**Study design**: Interrupted Time Series **Timeframe:** 2000-2007 **Intervention:** 2006 Guideline changes and an educational intervention to reduce the use of fluoroquinolones, carbapenems and 2nd and 3rd generation cephalosporins, enhanced infection control measures	Significant reduction in amount of and trends in cephalosporin consumption, no change in fluoroquinolone and carbapenem prescribing trends with increasing overall carbapenem use, significant increase in piperacillin/tazobactam amount and upwards trend	Ongoing ESBL outbreak terminated. Apart from this no change in rates of resistance to tested antibiotics in *E. coli*, *K. pneumoniae* or *P. aeruginosa* in blood isolates
Willemsen et al[150]	**Study design**: Interrupted Time Series **Timeframe:** 2004-2007 **Intervention:** 2006 IV to oral switching, new guideline, automatic advisory notes, prescriptions and feedback	Reduction in overall quinolone use	Reduction in upwards trend of quinolone resistance rates in *E. coli* isolates
Studies with *C. difficile* infection only as an outcome			
Jump et al[151]	**Study design**: Comparative Interrupted Time Series **Timeframe**: 2006-2011 **Intervention:** 2009 Implementation of an on-site infectious diseases service	Significant decrease in overall antibiotic administration, and tetracycline, clindamycin, co-trimoxazole, beta-lactam/beta-lactamase combination, and fluoroquinolone administration and trends	Significant reduction in the rate of positive C. difficile tests
McNulty et al[152]	**Study design**: Interrupted Time Series **Timeframe:** 1993-1995 **Intervention:** 1994	Significant reduction in cefuroxime use	Number of *C. difficile* infections in the 7 months after the policy was initiated was significantly less than the number in the 7 months before

Study	Intervention	Effect on prescribing	Effect on resistance
	Prioritising use of antibiotics that had less effect on gut bacteria		
Talpaert et al[153]	**Study design**: Interrupted Time Series **Timeframe:** 2005-2007 **Intervention:** 2006 Change in antibiotic policy in, prioritising 'low *C. difficile* risk' antibiotics and clinical reviews	Significant decrease in fluoroquinolone and cephalosporin consumption, no change in clindamycin, amoxicillin and co-amoxiclav use	Significant decrease in *C. difficile* infection in 12 months after intervention compared to 12 months before
Valiquette et al[154]	**Study design**: Interrupted Time Series **Timeframe:** 2003-2006 **Intervention:** 2003-2004 Change in antibiotic guidance aimed at reducing targeted high risk antibiotics and reduction durations of treatment	Significant reduction in cephalosporin, clindamycin, macrolide and ciprofloxacin consumption, a significant increase in moxifloxacin and piperacillin/tazobactam use	Significant reduction in *C. difficile* infection incidence and trends

1.3.10.1 *Insights from reviewing antibiotic interventions and their effect*

In summary, the evidence for antibiotic interventions reducing resistant infection or affecting microbiological outcome is mixed. It is worth noting the heterogeneity in results for what were apparently similar interventions – which may be due to local resistance patterns (e.g. differential prevalence of co-carriage of resistance-conferring mechanisms to multiple classes of drug), simple chance, or study design.

Multiple studies looked at interventions aimed at reducing cephalosporin use either alone[140,144,147] or in addition to reducing use of other antibiotics[130,131,135,136,141,143,145,149,153,154], with a common theme in these being a subsequent increase in piperacillin/tazobactam consumption[130,134,140,141,144,147,149,154]. Microbiological results of these studies were mixed - showed some impact on reducing resistance to cephalosporins or ESBL rates[131,140,144,147,148], though others found no evidence of effect[132,135]. Two studies found no evidence for change in piperacillin/tazobactam resistance patterns [140,148] whilst two found evidence for a reduction in [144,147] in piperacillin/tazobactam resistance, though the results from the Meyer et al[147] study was mixed- they saw a decrease in percentage of *K. pneumoniae* isolates that were piperacillin-resistant, but an increase in piperacillin-resistant *E.coli* isolates (though no overall change in the percentage that were resistant). The reason why swapping one broad-spectrum beta-lactam for another may reduce resistance rates is not immediately clear. Grohs et al[138] hypothesised that the effect was due to the activity and resistance selection in the gut. Indeed ceftriaxone is excreted in active form via the biliary tree, however piperacillin-tazobactam also reaches therapeutic concentrations in bile fluid[156], hence it's utility in the treatment of bilary sepsis[157].

Another reproducible finding was that interventions that reduce use of perceived *C. difficile* 'high risk' antibiotics (and mostly end up substituting their use for other 'low risk' antibiotics) saw reductions in *C. difficile* infection rates[134,136,151-154], highlighting the

importance of the impact of antibiotics on the microbiota, though one study did not find evidence of effect[132]. *C. difficile* infection appears to be driven by the circulation of high-virulence resistant strains, together with disruption in the host gut microbiota, leading to overgrowth and toxin production by *C. difficile* strains present in the gut. Thus changes in antibiotic use away from antibiotics that select for resistant strains, and disrupt the gut bacteria, could reasonably be expected to reduce incidence of infection, and indeed this was demonstrated by multiple studies. However it is worth noting that all the antibiotic interventions occurred concurrently with changes in infection control practices designed to reduce *C. difficile* transmission, and there may be significant confounding from this. Additionally, given the evidence for spread of epidemic strains of *C. difficile* infection[158,159], the reduction in *C. difficile* rates seen in some studies may be in part due to the end of the epidemic phase.

There is also reproducible evidence that changes in prescribing can affect resistance rates in *P. aeruginosa*[131,137,140,142,155] though two did not find evidence of effect[144,149]. *P. aeruginosa* has an excellent ability to persist in biofilms and colonise patients, and develop inducible resistance by upregulation of efflux systems. Reducing exposure to antibiotics that select for efflux pump upregulation, but do not penetrate biofilms and enable full eradication, or do not exhibit poor overall activity against *P. aeruginosa* (such as many cephalosporins, except the pseudomonal-active cephalosporins such as ceftazidime), could also be expected to reduce resistance levels in sampled colonising or infecting strains.

Lastly, MRSA appears to show some response to antibiotic policies in some of these studies[130,160,118,127], though others did not find evidence of effect[132-134,136,145]. Given that infection control measures have been shown to effectively limit or reduce MRSA spread and all the studies looking at MRSA had concurrent infection control measures or did not report

them, it is difficult to conclude whether it is the antibiotic policy or the infection control measures that had the effect.

In all, these results highlight that different pathogens may have markedly different behaviours in response to antibiotic changes, and also that markers of 'success' may have to differ depending on desired outcome. It may be possible to substantially reduce C. difficile rates with antibiotic changes, and MRSA rates with antibiotic changes combined with infection control measures. However for gram-negative Enterobacteriaceae, it may be that reducing the rate of increase is a more realistic aim. There are significant challenges in attempting to reduce the incidence of resistance in gram negative bacteria, rather than simply slowing the increase in resistance[161]. In these organisms, horizontal gene transfer is a major mechanism of resistance acquisition. Complex mechanisms can also prevent reversion to susceptible phenotype, such as plasmid toxin/antitoxin systems and compensatory mutations leading to lack of fitness cost. Therefore once a high-fitness, highly-spreading, endemic strain develops resistance, it may be extremely difficult to reverse this change, especially if alterations in antibiotic policy which switch, rather than reduce, antibiotic use, lead to increased use of an antibiotic which also selects for the resistant strain. Given that many epidemic strain plasmids in Enterobacteriaceae demonstrate multiple different resistance mechanisms, this is a significant issue. Cross-resistance to beta-lactams and trimethoprim has already been identified as a possible reason why some community policies restricting beta-lactam use may have had limited efficacy[162]. These complex genomic mechanisms of antibiotic resistance transmission suggest that perhaps our focus on controlling bacterial spread to combat antimicrobial resistance is suboptimal, and we should instead be designing strategies based on their ability to control spread at the dominant mode of transmission – be it transposon, plasmid, non-human-colonising bacterial gene 'donor', or high-fitness epidemic human pathogen[163].

The advantages of these studies in informing potential strategies to reduce resistance is that they look at real-world scenarios, using interventions that are achievable in the acute hospital setting. They study the real effects of changes in antibiotic use on resistance incidence in vivo, in hospital patients, in the complex hospital environment, thus taking into account complex factors such as interactions with exposure and transmission.

The limitations of these studies are also worth considering. One key limitation is that these studies are generally implemented in response to concerns about resistant infection – such as an outbreak of *C. difficile* or ESBL infections, or the site having above-average rates of resistance. Firstly, this means that there are often multiple, non-antibiotic measures that may be major contributors to any changes in resistant infection rates, such as infection control measures, or changes in staff behaviour. Secondly, the natural history of outbreaks mean that time alone and 'regression to mean' will make any interventions started during outbreak phase more likely to see reductions in incidence of the outbreak pathogen regardless of intervention. Indeed the Davey et al review highlighted that 'unplanned' interventions (ie. in response to outbreaks) were associated with markedly greater effect on microbial outcomes. Another limitation is that factors outside the hospital in question, such as outbreaks in the community or other institutions with high patient exchange, or changes in community prescribing, may influence resistance rates. The final limitation is that there is likely to be a significant publication bias towards studies that showed an effect on prescribing and reductions in resistance.

The studies highlight another issue with attempting to change antibiotic use – it is often difficult to simply reduce the use of a particular antibiotic; in reality what happens is that antibiotic use is simply transferred to other choices – a 'squeezing of the balloon' effect. It is much simpler to change antibiotic choice than reduce antibiotic use. Indeed there were no

studies with a resistance outcome that attempted to limit prescribing, or encourage non-antibiotic management.

1.4 Summary of literature review

In conclusion, there remain significant challenges in identifying clinical criteria that can assist the acute medical physician in objectively ruling out infection, and diagnosis remains one of clinical judgement.

There is evidence linking antibiotic consumption with resistance, and prior antibiotic exposure and resistance, though most studies look at the direct association between antibiotic and resistance to that antibiotic, and few look at cross-resistance. The strongest evidence is that reducing the number of patients exposed to an antibiotic is likely to be beneficial in reducing selection for resistance, but a very limited number of studies have demonstrated this successfully in the acute medical setting, with none studying clinical outcome satisfactorily. There is some evidence that shorter courses may reduce selection for resistance, and good evidence that shorter courses can be used safely. There is some limited evidence that using higher doses might reduce selection for resistance, with little data on clinical outcome.

In terms of studies which changed antibiotic prescribing, there is some evidence that changing guidelines away from 'high risk' antibiotics for *C. difficile* (such as cephalosporins and ciprofloxacin) can reduce *C. difficile* rates, but there are only a few studies that show any effect of prescribing changes on resistance in MRSA and Enterobacteriaceae.

In terms of research questions identified, there are two main areas. Firstly, there is an ongoing need to identify strategies that can reduce antibiotic exposure in the acute medical setting, without adverse impact on clinical outcome. Second, it would be useful to more comprehensively assess the overall resistance-selective effects of classes of antibiotics and

considering the effect of multiple different classes on resistance to an antibiotic, and vice versa, in vivo as cross-resistance, pharmacokinetic and subsequent ecological effects may have significant impact on overall resistance selective effects.

1.5 **Thesis Outline**

The aim of this thesis is to progress the current knowledge available to the acute medical physician in choosing antibiotic prescribing strategies that are most likely to be effective in reducing the spread of antimicrobial resistance, whilst still being safe for the patient.

In Chapter 2, I conduct a small study of antibiotic use in 297 admission to the acute medical service in the John Radcliffe Hospital, identifying that an Infectious-Diseases trained physician uses 30% less antibiotics than other physicians by starting fewer patients on antibiotics, and uses less broad spectrum antibiotics, but at the cost of more admissions to hospital and a longer length of stay. I interrogate electronic health record data of five years of acute medical admissions and see no evidence of differences in mortality between patients managed by the Infectious-Diseases trained physician or other teams. I identify that to conduct studies that aim to assess resistant infection as an outcome in the acute medical setting, it will be necessary to perform analyses using a much larger study size due to resistant infections being a relatively rare outcome.

In Chapters 4 and 5, I conduct two analyses of the accuracy of electronic health record data to inform the design of my future studies into antibiotics and resistant infections. In Chapter 3, I assess to what degree diagnostic codes can be used to accurately estimate Charlson comorbidities in a small Oxfordshire dataset of 284 patients, since this is an important confounder in risk-adjusted analyses of mortality and clinical outcome. I conclude that diagnostic codes assigned at discharge are relatively robust in estimating the comorbid state

of the patient at point of admission, and that using current methods, diagnostic codes assigned due to in-hospital complications that were not present at point of admission are only very rarely a cause for incorrect estimation of comorbidity.

In Chapter 4, I assess the degree to which diagnostic codes can be used to estimate cases of an infective disease, using infective endocarditis as a case study. I find that significant discrepancies exist between admissions with an 'endocarditis' diagnostic code, and confirmed clinical cases of endocarditis. I investigate the reasons for discrepancies, and suggest data curation steps that can used to improve estimation of cases from administrative data. I also show that there are significant limitations in using diagnostic codes to study the causative organisms.

These studies inform my work in Chapter 5, where I perform an analysis of prior antibiotic use in patients with *E. coli* and *K. pneumoniae* bloodstream infections, using linked electronic health record data and laboratory microbiology results. I find that broad-spectrum beta-lactam exposure and trimethoprim exposure are associated with beta-lactam resistance in these organisms. I find no evidence of association between duration of antibiotic exposure and development of resistance.

I conclude this thesis by discussing the clinical implications of my work to the acute physician making antibiotic prescribing decisions, to the hospital clinician designing antibiotic guidelines, and to the research community in designing future studies which aim to comprehensively identify prescribing strategies to reduce the development of antimicrobial resistance.

2 Chapter 2: Antibiotic use and clinical outcomes in the acute setting under management by an Infectious Diseases Acute Physician versus other clinical teams: a cohort study

2.1 INTRODUCTION

2.1.1 The research question

I have identified in Chapter 1 that there is limited data on how we can reduce antimicrobial prescribing safely in the acute medical setting. For certain presentations, there are guidelines to suggest conditions in which antibiotics can safely be withheld, such as cough or uncomplicated bronchitis. There are biochemical tests, such as procalcitonin, which can guide non-antibiotic management. But for all this, there is a lack of objective criteria which enable the clinician to reliably diagnose or exclude infection with confidence for the majority of infective presentations, and subjective clinical judgement, taking into account multiple clinical and social factors, must still be relied upon. I have also shown evidence that even when objective criteria are applied, expert opinion can often differ about the presence of infection, especially in older adults. I have discussed a lack of data about antibiotic use in the acute medical setting, with studies largely limited to the emergency department, or looking only at patients admitted to medical wards, neither of which completely reflects the setting I am studying. Finally, I have highlighted a lack of data about whether antibiotic reduction can be achieved in the emergency setting without clinical harm or other adverse consequences.

In this Chapter I aim to study how antibiotics are used in acute medicine, look for evidence that antibiotic use can be reduced in a real-life hospital environment in an acutely unwell, heterogenous group of patients with uncertain diagnoses. I also aim to quantify this possible

reduction, look for any evidence of adverse patient outcomes from any reductions, and look into how they can be achieved.

2.1.2 Can increased training/expertise in infection guide safe reductions in antibiotic use?

I discussed in Chapter 1 the difficulty in accurately identifying infection, the limitations of objective criteria, and the variability in physician evaluation of infection. One possible way of improving the diagnosis (and ruling out) of infection in the acute setting may be the use of expert input from Infectious Diseases trained Physicians. Previous studies have shown that management input from an Infectious Diseases Physician (IDP) can reduce antibiotic use in the acute hospital setting. Studies have demonstrated that IDP input for patients managed under other acute physicians is associated with shorter durations of treatment, with more patients having treatment stopped or shortened[164]. IDP input has also been associated with reduced length of stay[165], costs of antibiotic therapy[166,167], and improved clinical outcome ([166,167], also reviewed in[168,169]). It is worth highlighting however that all of these studies have assessed the effect of additional IDP input to the existing medical team, at a time when the patient is already admitted to hospital and has had investigations, and there has been time to form a comprehensive diagnosis. They have not studied the effect of the IDP on the decision to initiate therapy in a patient at a time of clinical uncertainty.

A few studies have compared management of acute medical patients by Infectious Disease and non-Infectious Disease trained hospitalists[170,171]. Eron et al looked retrospectively at the management of patients with diagnosed infections, showing shorter length of stay and better patient satisfaction, but did not examine quantity of antibiotic use[171], whilst Borer et al compared management of febrile syndromes between patients managed by IDP hospitalists

and non-IDP hospitalists, and showed improved antimicrobial appropriateness and accuracy of diagnosis, but did not examine length of stay or mortality[170].

With an onus upon all physicians to reduce antibiotic use, it is desirable to examine further what strategies IDPs may be using to reduce antibiotic use that can be subsequently employed by general medical physicians themselves.

2.1.3 **Study design considerations**

The goal of my study was identify whether general medical physicians could make significant, safe antibiotic reductions, and to assess the magnitude of this achievable reduction in an entire, mixed patient cohort from point of referral to the acute medical service, rather than in selected conditions. I also wished to investigate whether there was any evidence for adverse effects from lower antibiotic use on patient outcome.

The structure of the acute medical inpatient service in my institution, the John Radcliffe Hospital, enables a comparison between the antibiotic use of an Infectious Diseases Acute Physician (effectively an IDP) and other physicians. In this service, acute, unselected medical patients are admitted, depending on calendar date and time of day, under the care and management of a designated Consultant physician and their team, who rotate on a regular basis. The Consultants come from a range of specialities, and a number of these will be IDPs. I made the decision to compare antibiotic use on a team/managing physician level given both previously published work suggesting it is the "senior doctor who ultimately decides what antimicrobial is prescribed"[172], and extensive experience in the service together with consultation from colleagues, who confirmed anecdotally that local experience reflected this statement.

I had available data in the form of a prospectively collected benchmarking audit I conducted to investigate antimicrobial prescribing in the acute medical service over 1 week. From this I was able to perform an explanatory post-hoc analysis to compare antibiotic use between IDP and non-IDP physicians.

I was aware that this data would be of insufficient size to be able to detect anything but extremely large differences in mortality and clinical outcome, so to further investigate outcome between IDP and non-IDP management with greater statistical power, I also analysed a 3 year dataset of routine electronic health records for mortality and length of stay (although patient-level prescribing and clinical response data was not available in this dataset, only becoming available in routine electronic records after I conducted this study).

My primary objective was therefore to assess the difference in total amount of antibiotic used between IDP-led and non-IDP-led teams. My secondary objectives were to assess whether there was any evidence that differential antibiotic use led to adverse clinical outcomes or increased length of stay in the different teams, and to identify specific differences in antibiotic prescribing strategies.

2.2 **METHODS**

2.2.1.1 ***Clinical and Prescribing Data***

2.2.1.2 ***Antibiotic data and structure of the medical teams***

Antibiotic prescribing data was collected prospectively on all acute admissions to the medical service in a UK tertiary care centre (John Radcliffe Hospital, Oxford) from 08:00 16th April–08:00 23rd April 2013) by the lead author, an active physician in the department, but not working during this period. Data was collected as a benchmarking audit of antimicrobial prescribing. In this service, patients are admitted from primary care and Emergency

Department referrals, and managed under an on-call consultant Acute Physician and their team, who share an on-call team rota with three shifts per day (08:00-15:59, 16:00-20:59, night shift 21:00-07:59). The team make initial management decisions (including antibiotic prescribing) before or during a consultant ward round of all newly-admitted patients. After initial care a small proportion of patients are transferred for operational reasons to the nearest available bed under any team or to other non-acute specialities (<5%); the majority are managed under admitting team (**Figure 7**). The acute team usually consists of a consultant physician (senior), and three physicians in training with one to seven years of post-qualification experience (juniors). An IDP with triple accreditation in Infectious Diseases, Microbiology and General (Internal) Medicine performed usual clinical duties during the audit period. Acute Physicians were informed antibiotic prescribing audits were ongoing, but were not aware of exact audit dates. All patients who had a documented referral to medical team and were reviewed by them were included, even if they were sent home from the Emergency Department without attending a medical ward.

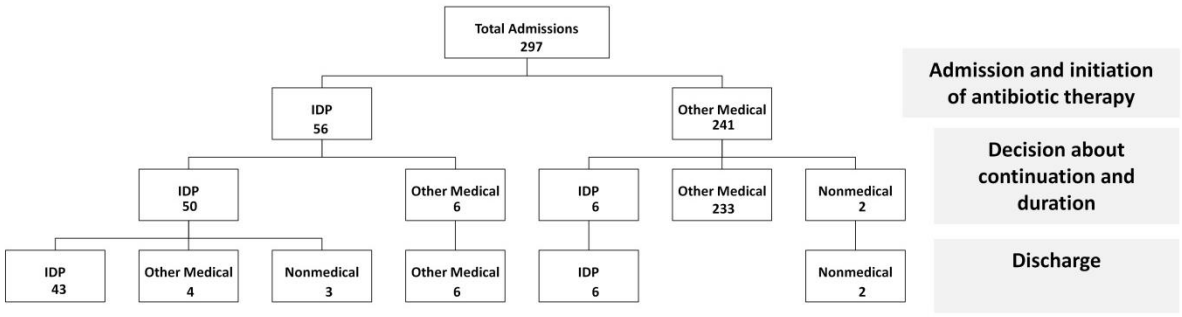


Figure 7: Patient Admissions and managing Acute Physician from admission to discharge

2.2.1.3 *Data collected*

Data was collected on antibiotic use, managing team, principal diagnosis and factors affecting antibiotic prescribing including admission timing, allergies, and comorbid status. Principal diagnosis was copied from the attending physician, not made retrospectively. Infection likelihood was graded by the lead author based on the consultant physician's documented review using the objective criteria: high likelihood - most likely diagnosis documented was infection; medium – infection was among many differential diagnoses documented; and low – list of differential documented diagnoses did not include infection. Compliance with local empirical treatment guidelines was also recorded. First antibiotic was compared to the guidance for the documented working diagnosis and judged inappropriate if it did not match. Appropriateness of duration was assessed for completed courses of empirical therapy without documented complications or changes in diagnosis. Clinical outcomes collected were mortality (through 30 days post-discharge), readmission, escalation/restarting antibiotic treatment, and disease-related complications (**Table 2**). A composite clinical outcome of 'treatment failure' (any of these outcomes) was also considered. Delays in treating patients with sepsis were also recorded. Data was extracted by review of drug chart, clinical and electronic notes by the lead author.

A larger 3-year dataset of hospital electronic health records was also extracted from the Infections in Oxfordshire Research Database (IORD), for all patients admitted under the Acute Medicine service from 00:01 on 1st January 2012 to 23:59 on 31st December 2014, including managing consultant, ICD-10 diagnosis codes, length of stay, mortality and readmissions. Patient-level prescribing and clinical response data was not available in this dataset. During this period, the IDP performed clinical duties in both the Acute Medicine service, and other departments together with periods of leave, thus admitting approximately 1% of patients in this dataset.

In the audit, antibiotic use was calculated using several metrics using previously published definitions[173], and classified according to physician team who managed the patient at admission. It included antibiotics to be taken post-discharge and antibiotics used if transferred to non-acute medical specialties (including intensive care units). Bed-days were calculated from changes in calendar date, counting patients admitted and discharged on the same day as one day. The treatment-related length-of-stay was duration until recorded as 'medically fit for discharge'. The primary outcome metric of days of therapy (DOT) per patient admission was chosen as it best reflected physician prescribing decision-making, and had fewer potential confounding factors, namely local formulary choice mismatches with the WHO-standard defined daily dose (DDD)[174] and changes in length-of-stay; it is a metric choice supported by other prescribing analyses using regression modelling[173,174]. Days of therapy counts each antibiotic received for one day as 1 DOT (so 2 antibiotics for 1 day = 2 DOT). I also considered length of therapy (LOT: total calendar days on which one or more antibiotics were taken)[173-175].

Table 2: Disease-Specific Complications collected

Infection Site	Complication
Lower respiratory tract infection or pneumonia or infectious exacerbation of COPD	Empyaema, pleural effusion, abscess
Urinary tract infection	Pyelonephritis
Meningitis	Obstructive hydrocephalus
Cellulitis	Requirement for debridement
Gastrointestinal infection	Perforation, abscess, need for abdominal surgery

COPD=Chronic obstructive pulmonary disease

2.2.2 Comparison of clinician-collected Charlson comorbidities and coding-based assessment

Given I planned to use electronically-collected data to measure comorbid status in my 3 year dataset of electronic health records, I performed a comparison of clinician-collected data on

presence of Charlson comorbidities[176] at point of admission, and presence of comorbidities as assessed using presence of diagnostic codes representing these comorbidities assigned to the matched admission using previously published methods[177]. This data is presented in detail in Chapter 3. In brief, diagnostic coding-based assessments of Charlson comorbidities had an overall sensitivity of 84% for predicting admission comorbidities, specificity of 99%, positive predictive value (PPV) of 92% and negative predictive value (NPV) of 99%. As such, I judged that it was reasonable to use electronic health record data in my 3 year dataset to measure comorbid status.

2.2.3 **Statistical analysis**

I hypothesised, based on small pilot data, that IDP management would lead to 30% less total antibiotic use, with no difference in clinical adverse composite outcome. 367 patients provided at least 80% power to detect a reduction in overall antibiotic use from 300 to 210 DOT/100 admissions (30% reduction) based on 10000 simulations from a Poisson distribution assuming that 20% patients were admitted under IDP during audit period, overall 30% patients received antibiotics and two-sided alpha=0.05. Acute medicine admits 300-400 patients per week; one week was therefore chosen as a representative audit sample including out-of-hours and weekend prescribing.

Baseline characteristics between IDP and non-IDP groups were compared using Wilcoxon ranksum tests for continuous and Pearson chi-squared or Fisher's exact tests for categorical factors. Antibiotic prescribing was modelled as a two-step process (initiation and subsequent decision about total quantity), representing clinical experience and national prescribing guidance[178], using a zero-inflated Poisson model. A zero-inflated negative binomial model was also considered; however, estimates were very similar and there was no evidence of

over-dispersion in the data which would favour a zero-inflated negative binomial model. A standard negative binomial model was also evaluated and performed poorly compared to models with a zero-inflated component, due to the high proportion of patients receiving no antibiotics. Because there was clear separation between DOT in those receiving antibiotics and the zero DOT in those not receiving antibiotics, and because I was concerned about the possibility of non-linear effects of some continuous predictors (particularly age and laboratory test results), predictors of receiving an antibiotic prescription or not were first identified using multivariable fractional polynomial logistic regression with backwards elimination (exit p=0.05; stata mfp; based on the 20 factors in **Table 3**). Factors retained in this model were included in the zero-probability component of the zero-inflated Poisson regression, with predictors of antibiotic quantity identified using a second phase of backwards elimination on the same factors (exit p=0.05). In regression models, DOT and length-of-stay were truncated at their 95th percentiles (18 and 17 respectively) to avoid undue influence from outlying observations leading to over-fitting. A small number of patients did not have any biomarkers of infection measured (19/297); only available data was used in the regression analysis (complete-case analysis). Risk-adjusted 30-day mortality was assessed using a multivariable fractional polynomial logistic model (backwards elimination, exit p=0.05). This analysis was repeated in a larger three-year dataset of 47585 admissions to acute medicine 2012-2014 (90% power to detect an IDP-associated mortality increase from 6% to 11%, assuming IDP saw 1% admissions). Analysis was performed using STATA 13.1.

2.3 **RESULTS**

2.3.1 **Patients managed under IDP received approximately 30% less antibiotics overall, due to fewer patients being given antibiotics, and shorter antibiotic courses**

During a one week period, the IDP-led team admitted 56 patients, and non-IDP Acute Physician teams admitted 241 patients (**Figure 7**). Teams admitted similar patients, except IDP patients had slightly lower white cell counts (WCC) and were more likely to be admitted with a frailty syndrome (**Table 3**). Group metrics showed the IDP-team used 173 Days of Therapy (DOT) per 100 admissions versus 282 DOT/100 admissions in the non-IDP group, an (unadjusted) reduction of 39% (**Table 4**). A similar percentage reduction was seen in all metrics assessed. 14/56 (25%) IDP patients were given an antibiotic versus 85/241 (35%) non-IDP patients.

Table 3: Patient characteristics at presentation to the acute medical service

Characteristics	Non-IDP (N=241) N (%) or median (IQR)	IDP (N=56) N (%) or median (IQR)	p
Age	72 (52-82)	79 (62-83)	0.15
Female	137 (57)	30 (54)	0.66
Charlson score	1 (1-2)	1 (1-2)	0.97
Ischaemic heart disease	34 (14 %)	6 (11%)	0.50
Congestive cardiac failure	18 (7%)	5 (9%)	0.71
Pulmonary disease	64 (27%)	10 (18%)	0.18
Cerebrovascular disease	24 (10%)	3 (5%)	0.44
Dementia	13 (5%)	7 (12%)	0.06
Renal disease	25 (10%)	6 (11%)	0.94
Liver disease	5 (2%)	0 (0%)	0.59
Cancer	19 (8%)	5 (9%)	0.80
Immunosuppression*	7 (3%)	4 (7%)	0.13
Sepsis **	20 (8%)	5 (9%)	0.88
Community antibiotic therapy	39 (16%)	11 (20%)	0.53
Pyrexia on admission	17 (7%)	5 (9%)	0.63
C-reactive protein	14 (3-60)	14 (5-70)	0.94
White cell count (10^9/l)	**8 (7-11)**	**8 (6-10)**	**0.03**
Weekend admission	57 (24%)	9 (16%)	0.22
Night-time admission	58 (24%)	17 (30%)	0.33
Admission with frailty syndrome* **	**28 (12%)**	**12 (21%)**	**0.05**

** Immunosuppression defined as: HIV infection, haematological malignancy, other malignancy, renal failure, previous transplant, chemo/radiotherapy in past 5 years, immunosuppressive drugs, systemic corticosteroids (0.5mg/kg/day for >14 days)*

*** Sepsis defined as per the American Society of Critical Care Medicine as fulfilling Systemic Inflammatory Response Syndrome (SIRS) criterion of 2 or more of: respiratory rate>20, pulse>90, leucocytes<4 or >12, temperature<36 or >38'c with an infective source.*

**** Frailty syndrome as defined by the British Geriatric Society[179] – falls, immobility, delirium/dementia, polypharmacy, incontinence, end-of-life care.*

Note: P values calculated using ranksum tests for continuous variables and chi-squared tests for categorical variables, unless any cell number was <5 or cell percentage <5% in which case Fishers exact test was used.

IDP=Infectious Diseases Physician.

Table 4: Antibiotic use according to managing physician across a range of metrics

Metric	Non-IDP (241)	IDP (56)	All		
Group metrics				Unadjusted RR (95% CI)	p
Days Of Therapy (DOT)/100 admissions	282	173	261	0.61 (0.50-0.76)	<0.001
Defined Daily Doses (DDDs)/100 admissions	340	227	320	0.67 (0.55-0.80)	<0.001
Broad-spectrum DOT/100 admissions	169	98	156	0.58 (0.44-0.77)	<0.001
Length Of Therapy (LOT)/100 admissions	210	129	195	0.61 (0.48-0.78)	<0.001
DDDs/100 bed-days	66	38	60	0.47 (0.31-0.70)	<0.001
Patient-level metrics	n (%) or median (IQR)	n (%) or median (IQR)		Adjusted OR /RR (95% CI)	p
Given an antibiotic*	85 (35%)	14 (25%)	99 (33%)	0.25 (0.07-0.84)	0.03*
DOT**	0 (0-5)	0 (0-0.5)	0 (0-5)	0.71 (0.54-0.93)	0.01**
DDDs**	0 (0-5.25)	0 (0-0.13)	0 (0-4.5)	0.67 (0.53-0.90)	0.006 **
LOT**	0 (0-5)	0 (0-0.5)	0 (0-3)	0.69 (0.52-0.94)	0.02**
DOT if started on an antibiotic	6 (5-9)	6 (3-7)	6 (5-9)	-	-
LOT if started on an antibiotic	5 (4-7)	4 (2-6.5)	5 (3-7)	-	-
Broad-spectrum*·*** antibiotic given	70 (29%)	11 (20%)	81 (27%)	0.53 (0.19-1.52)	0.24*
Broad-spectrum antibiotic DOT**	0 (0-2)	0 (0-0)	0 (0-1)	0.75 (0.54-1.03)	0.08**
Broad:narrow ratio	408/271 (1.51:1)	55/42 (1.31:1)	463/313(1.48:1)	-	-
Given IV antibiotic*	52 (22%)	8 (14%)	60 (20%)	0.39 (0.12-1.27)	0.12*
IV DOT**	0 (0-0)	0 (0-0)	0 (0-0)	0.76 (0.49-1.18)	0.23**
IV DOT if given IV	2 (1-3)	1 (1-4.5)	2 (1-4)	-	-

** from multivariable logistic regression model based on backwards elimination from IDP plus **Table 3** factors.*
*** from multivariable zero-inflated Poisson regression models based on backwards elimination from IDP plus **Table 3** factors (see Methods). **Table 5** presents the full multivariable model for DOT; predictors were similar for DDDs and LOT with the only differences being that an admission at the weekend was additionally associated with greater DDDs, and Charlson Score was not associated with DDDs; and the only factors associated with greater LOT were male sex, sepsis, and higher CRP on admission. Predictors for giving a broad spectrum antibiotic and being given an Iv antibiotic were immunosuppression, higher CRP and WCC on admission, with predictors of higher broad spectrum DOT being pyrexia, higher CRP, female sex, age, deprivation index and admission at night, and predictors of greater IV DOT were sepsis, higher CRP, deprivation index and female sex.*
****Broad-spectrum antibiotic: co-amoxiclav, ceftriaxone, meropenem, gentamicin, clindamycin, ceftazidime, ciprofloxacin, piperacillin/tazobactram*
Note: IDP=Infectious Diseases Physician. OR=odds ratio, RR=rate ratio. IV=intravenous.

2.3.2 Multivariate analysis adjusting for patient case mix confirms IDP management associated with lower antibiotic use

In a patient-level risk-adjusted model (see Methods, **Table 5**), IDP management was associated with a significantly lower odds of initiating antibiotics (adjusted p=0.03) and fewer DOT (p=0.01) suggesting that the lower antibiotic use in the IDP group was not simply an artefact of case mix. Patients presenting with sepsis or pyrexia, immunosuppressed or frail patients, those with higher C-reactive protein (CRP) or WCC at admission, and those who had received community antibiotic therapy were more likely to start antibiotics in hospital (**Table 5**). Factors associated with greater DOT were male sex, older age, sepsis, higher CRP on admission, lower Charlson Score and admission during the night.

Table 5: Independent predictors of Days-on-Therapy (DOT) in a zero-inflated Poisson model

	Factor	Adjusted OR (95% CI)	P
Association with starting an antibiotic	Management under IDP	0.32 (0.10-0.99)	0.05
	Presentation with frailty syndrome	3.87 (1.41-10.67)	0.01
	Received community antibiotics	10.57 (3.91-28.60)	<0.001
	CRP on admission (per 1 mg/dl higher)	1.02 (1.02-1.03)	<0.001
	Immunosuppression	49.12 (2.85-847.89)	0.007
	White Cell Count on admission (per 1^9/L higher)	1.22 (1.11-1.34)	<0.001
	Factor	Adjusted RR (95% CI)	
Association with greater days on therapy (DOT) per admission	Management under IDP	0.71 (0.54-0.93)	0.01
	Female	0.77 (0.65-0.92)	0.003
	Age (per 10 years older)	1.08 (1.02-1.13)	0.005
	Charlson score (per 1 unit higher)	0.94 (0.90-0.99)	0.01
	Sepsis	1.38 (1.15-1.65)	0.001
	Night admission	1.40 (1.18-1.67)	<0.001
	CRP on admission (per 10 mg/dl higher)	1.02 (1.00-1.03)	0.02
	Presentation with frailty syndrome	0.77 (0.62-0.97)	0.02

*Note: Sepsis and pyrexia perfectly predicted antibiotic use and so therefore could not be included in the zero-component of the model. No other factors in **Table 3** were independently associated. CRP=C-reactive Protein. IDP=Infectious Diseases Physician. OR=odds ratio, RR=rate ratio.*

2.3.3 No evidence of differing antibiotic spectrum, route, choice, diagnosis treated, or guideline compliance between non-IDP and IDP teams

There was no evidence of a difference in number of patients started on a broad-spectrum antibiotic (adjusted p=0.24), broad-spectrum antibiotic DOT (p=0.08), number of patients started on an IV antibiotic (p=0.12) or IV DOT (p=0.23). The reduction in total antibiotic use

was not due to reduced use of antibiotic combinations; analysis by total length of therapy (which counts days on single or combination therapy as a single day) also showed a 39% unadjusted total reduction (129 vs 210 LOT/100 admissions) (**Table 4**). Antibiotic choice and diagnosis treated were also similar between groups (**Table 6** and **Figure 8**). There was no evidence of differences between IDP and non-IDP groups in compliance with guidelines for first prescription (14/14 (100%) vs 78/85 (92%) prescriptions compliant respectively, p=0.59), compliance with guideline duration for uncomplicated infection without change in diagnosis (4/5 (80%) vs 39/44 (89%) completed courses compliant respectively, p=0.58) or adherence to documenting a post-prescription review (9/12 (75%) having a documented review in the IDP group and two decisions to stop (22%), compared to 47/62 (76%) reviews the non-IDP group, with 11 decisions to stop (21%), p>0.9). As numbers were small, data was insufficient to conclude that prescribing quality was similar between IDP and non-IDP teams, but there was no signal that the significant differences observed in the total volume of antibiotics prescribed could be clearly attributed to these factors.

Table 6: Working Diagnoses treated and antibiotics used

Working Diagnosis*	Non-IDP(N=85) N (%)	IDP (N=14) N (%)	p**
Chest	36 (42)	5 (36)	0.64
Urinary tract	14 (16)	4 (29)	0.28
Unknown	8 (9)	0 (0)	0.60
Soft tissue	7 (8)	1 (7)	0.69
Other	6 (7)	1 (7)	1.00
Meningitis/encephalitis	5 (6)	0 (0)	1.00
Sepsis	3 (4)	2 (14)	0.15
Multiple	3 (4)	0 (0)	1.00
Neutropaenic sepsis	2 (0)	0 (0)	1.00
Gastrointestinal	1 (1)	0 (0)	1.00
Antibiotic given			
Co-amoxiclav	56 (66)	9 (65)	0.91
Clarithromycin	11 (13)	4 (29)	0.22
Ceftriaxone	16 (19)	3 (21)	0.73
Amoxicillin	7 (8)	1 (7)	1.00
Flucloxacillin	5 (6)	1 (7)	1.00
Meropenem	2 (2)	0 (0)	1.00
Metronidazole	4 (5)	1 (7)	0.54
Doxycycline	4 (5)	0 (0)	0.54
Clindamycin	3 (4)	1 (7)	0.46
Gentamicin	11 (13)	1 (7)	1.00
Ciprofloxacin	2 (2)	0 (0)	1.00
Nitrofurantoin	5 (6)	1 (7)	1.00
Moxifloxacin	4 (5)	0 (0)	0.54
Vancomycin	2 (2)	1 (7)	1.00
Piperacillin-tazobactam	6 (7)	1 (7)	1.00
Trimethoprim	2 (2)	0 (0)	0.74
Clindamycin	2 (2)	0 (0)	0.74
Other	2 (2)	0 (0)	0.74

**Working Diagnoses: Unknown = older adult with functional decline and chest/urine infection suspected but no clear source localising infection, Other=dental infection, ear infection or antibiotic use for gastrointestinal bleed prophylaxis, Multiple = clear localising symptoms/signs for more than one source*
***calculated using Chi-squared test or Fishers exact test if cell number was <5 or cell percentage <5*

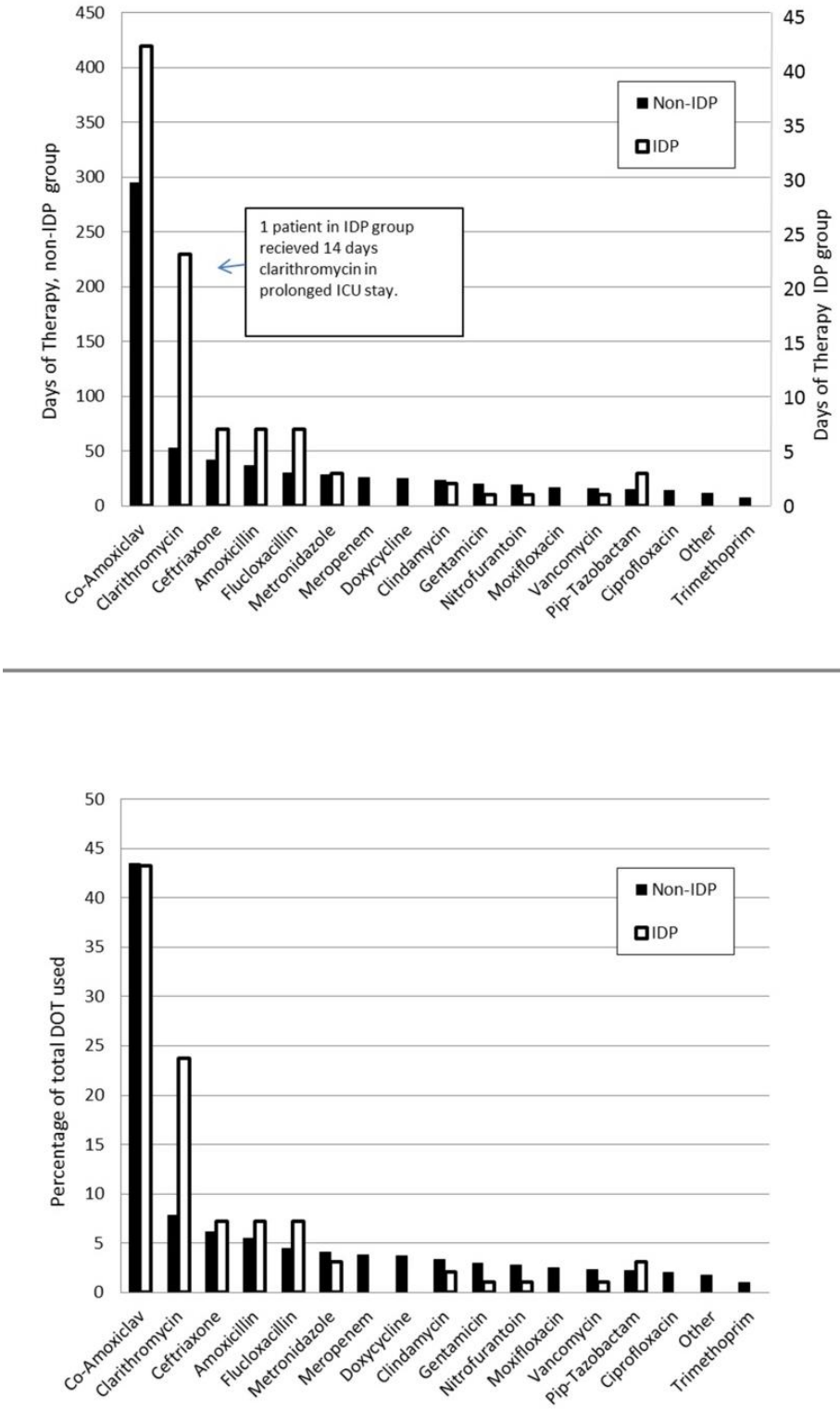


Figure 8: Antibiotic class used by IDP and non-IDP physicians

2.3.4 **A 'hold-and-observe' strategy in stable patients where the diagnosis is not established may contribute to reduced IDP antibiotic use.**

There was no difference in antibiotic prescription rates between IDP vs non-IDP groups in perceived high-risk patients (classified according to presenting features as having a high likelihood of infection, sepsis or immunosuppression), or in patients with low likelihood of infection. However, there was a difference in antibiotic use in cases of uncertain infective diagnosis without adverse features (**Table 7** and **Figure 9**). In the IDP group, 2 (13%) of 16 patients in this group were started on antibiotics on admission, versus 31/69 (45%) in the non-IDP group (p=0.02). Two of the 14 patients in the IDP group who had antibiotics initially held subsequently had antibiotics started for the presenting issue after a period of observation, one for possible bronchitis and one for a possible urinary tract infection in the absence of conclusive culture result. Given the difference in prescribing in patients of uncertain diagnosis, I also looked specifically at this group and found no evidence of difference in clinical outcome (**Table 8**).

Table 7: Likelihood of starting antibiotics on day of admission in IDP and non-IDP teams, by likelihood of infection and risk of delaying antibiotics

Likelihood of infection as per documented review**	Risk of delaying antibiotics (presence of sepsis/immunosuppression)	Non-IDP (N=241) Number started on antibiotics on day of admission/total (%)	IDP Number started on antibiotics on day of admission/total (%)	p*
High	High	17/17 (100%)	5/5 (100%)	-
	Low	22/27 (81%)	4/5 (80%)	1.00
Medium	High	7/9 (78%)	1/1 (100%)	1.00
	Low	**31/69 (45%)**	**2/16 (13%)**	**0.02**
Low	High	0/0 (0%)	0/0 (0%)	-
	Low	1/119 (1%)	0/29 (0%)	1.00

** Fishers exact test*
***Based on documented Consultant review: High = infection most likely diagnosis, Medium = infection on list of differential diagnoses, Low = infection not on list of differential diagnosis.*
Note: IDP=Infectious Diseases Physician.

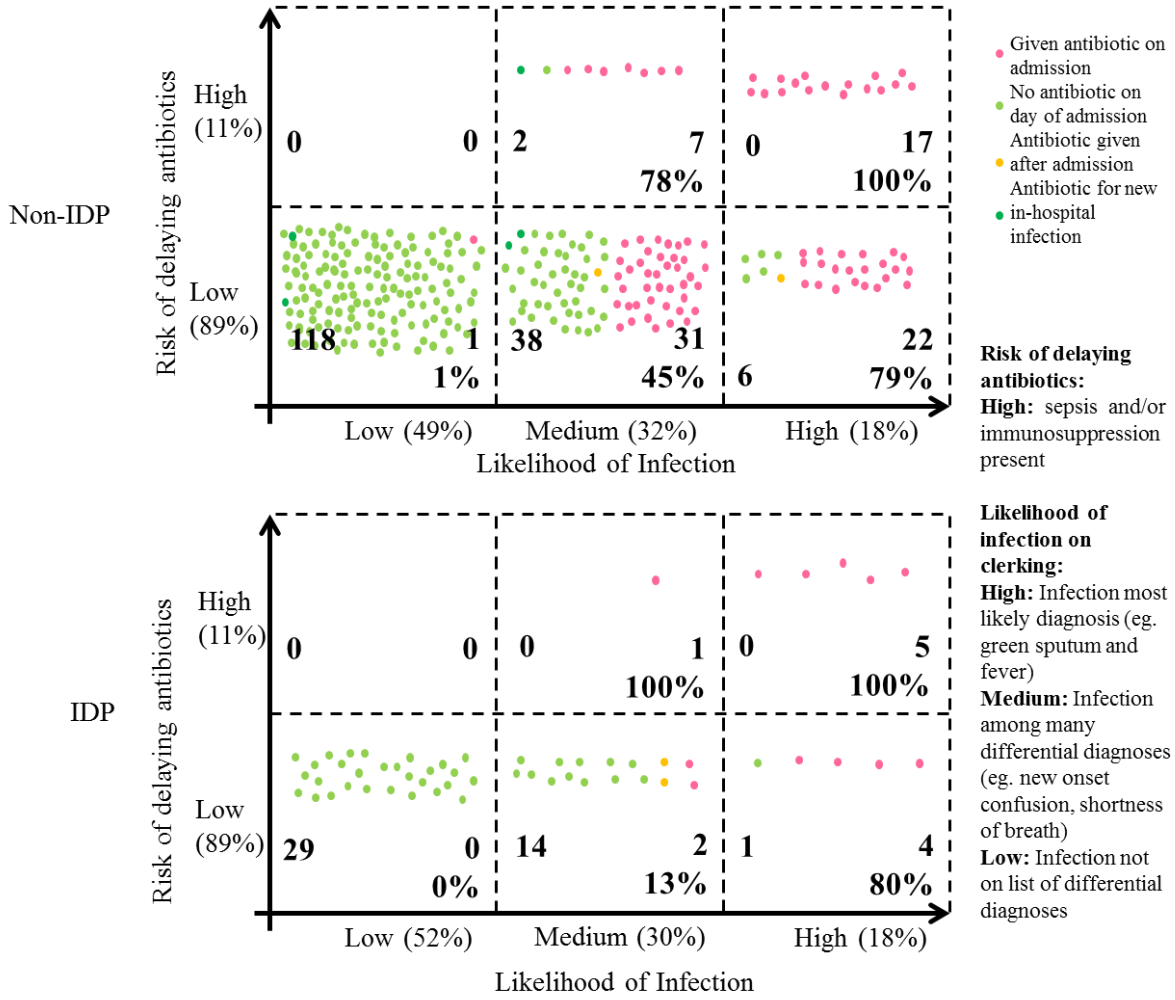


Figure 9: Likelihood of starting antibiotics on day of admission in IDP and non-IDP teams, by likelihood of infection and risk of delaying antibiotics

2.3.5 IDP management was not associated with delays in treatment, increased mortality, or treatment failure, but was associated with longer length of stay

There was no evidence that management under IDP was associated with risk-adjusted 30-day all-cause mortality or the composite 'treatment failure' outcome (adjusted p>0.5; **Table 8**). However, with relatively small numbers 95% confidence intervals were wide. There was no evidence of delays in treating sepsis, with of 11/20 non-IDP (55%) and 4/5 (80%) IDP

patients presenting with sepsis based on objective criteria[180] receiving antibiotics in <1h (p=0.62).

However, IDP management was associated with a slight, though significant, increase in length-of-stay (adjusted p=0.007; **Table 8**). One of the main contributors was an increased odds of overnight admission in the IDP group, with 49/56 (88%) patients admitted overnight versus 168/241 (70%) non-IDP patients (adjusted p=0.03). This was consistent with the previously-noted 'hold and admit' strategy of the IDP, versus a shorter length of stay 'prescribe and discharge' strategy in non-IDP physicians.

Table 8: Clinical outcomes including mortality, complications and admissions over one week audit and three years administrative data

Clinical Outcome	Non-IDP n (%) or median [mean] (IQR)	IDP n (%) or median [mean] (IQR)	Total n (%) or median [mean] (IQR)	Adjusted OR/RR* (95% CI)	p*
One week audit: all patients	(n=241)	(n=56)	(n=297)		
30-day mortality	36 (15%)	7 (13%)	43 (15%)	1.36 (0.53-3.54)	0.52
Escalation of therapy	12 (5%)	3 (5%)	15 (5%)		
Disease-specific complications	2 (1%)	0 (0%)	2 (1%)		
ICU admission	4 (2%)	2 (4%)	6 (2%)		
Readmission	50 (21%)	10 (18%)	60 (20%)		
Composite outcome	87 (36%)	19 (34%)	106 (36%)	1.21 (0.60-2.48)	0.59
Admitted overnight	168 (70%)	49 (88%)	217 (73%)	3.53 (1.24-10.03)	0.03
Length of stay	2 [5.2] (2-6)	4 [5.9] (3-6)	3 [5.3] (2-6)	1.19 (1.05-1.36)	0.007
Treatment-related length of stay	2 [4.2] (2-5)	3 [5.0] (2-6)	3 [4.3] (2-5)	1.27 (1.11-1.47)	0.001
One week audit: patients of uncertain diagnosis	(n=78)	(n=17)	(n=95)		
30-day mortality	11 (14%)	3 (18%)	14 (15%)	1.16 (0.26-5.17)	0.85
Composite outcome	31 (40%)	6 (35%)	37 (39%)	0.99 (0.29-3.45)	0.99
Administrative data, 1 Jan 2012-31 Dec 2014	(n=47,108)	(n=477)	(n=47,585)		
30 day mortality	2987 (6.3%)	27 (5.7%)	3,014 (6.3%)	0.92 (0.62-1.37)	0.68
Admitted overnight	37,329 (79%)	397 (83%)	37,726 (79%)	1.55 (1.20-2.01)	0.001
Length of stay	3 [6.8] (2-8)	4 [7.7] (2-8)	3 [6.8] (2-8)	1.15 (1.11-1.19)	<0.001

** Multivariable regression: One week dataset: C-reactive protein (CRP), white cell count (WCC) and Charlson score independently associated with 30 day mortality. Sepsis, Charlson score and admission with a frailty syndrome independently associated with adverse composite outcome. Charlson score, age and later time of day independently associated with admission. Charlson score, age, presentation with a frailty syndrome, community antibiotics, WCC and admission during a weekday independently associated with longer length of stay. Three-year dataset: Charlson score, age, male gender and non-weekday-admission independently associated with mortality, Charlson score, age hour-of-admission and non-weekday-admission independently associated with admission overnight, Charlson score, female, age, hour-of-admission and non-weekday-admission independently associated with longer length of stay.*
Note: IDP=Infectious Diseases Physician. OR=odds ratio, RR=rate ratio. ICU=intensive care unit.

To investigate clinical outcome associated with IDP management further, and explore whether these findings could be replicated in a larger dataset, I also looked in a three-year administrative dataset of over 47,000 admissions (2012-2014) (**Table 8**). Similar to my one-week dataset, this comprised patients admitted to the acute, unselected medical take, during which time the same consultant teams were operating with broadly the same antibiotic policy. Patient characteristics available in both the 1 week and 3 year datasets were broadly similar in terms of age, gender, Charlson Score (as calculated using hospital ICD-10 coding in the 3-year dataset) and admission at a weekend(**Table 9**).

Table 9: A comparison of available patient characteristics in 1 week and 3 year datasets

Characteristics	1 week (N=297) N (%) or median (IQR)	3 year (N= 47585) N (%) or median (IQR)	p
Age	73 (53-83)	74 (56-84)	0.34
Female	167 (56%)	24775 (52%)	0.16
Charlson score*	1 (0-2)	1 (0-2)	0.33
Weekend admission	66 (22%)	11963 (25%)	0.28

* calculated from hospital ICD-10 coding for the 3 year dataset

There was no evidence of IDP-associated excess mortality risk in this much larger dataset (adjusted p=0.68, **Table 8**; full regression model **Table 10**). Similarly to the 1 week dataset, IDP management was associated with increased likelihood of overnight admission and longer length-of-stay (adjusted p<0.001, **Table 8**). There was no evidence that the relationship between IDP management and these clinical outcomes depended on age, Charlson score or time/date of admission (heterogeneity/interaction p>0.05). Whilst prescribing and patient clinical data was not available in this larger dataset, these findings increased my power to detect differences in clinical outcome, and suggest the increased likelihood of admission and longer length of stay seen with IDP management were not restricted to my smaller 1 week dataset.

Table 10: Association of factors with in-hospital mortality 1st Jan 2012 – 31st Dec 2014 in 47,585 patients admitted to Acute Medicine

Risk Factor	OR (95% CI)	P
Management under IDP	0.92 (0.62-1.37)	0.68
Female	0.86 (0.79–0.93)	0.01
Charlson Score (square root transformed: per 1 unit higher)	42.1 (31.7-56.0)	<0.001
Age (per year older)	1.04 (1.04-1.04)	<0.001
Non-weekday-admission	1.16 (1.07-1.26)	<0.001

2.4 DISCUSSION

2.4.1 Key findings

This analysis of antibiotic prescribing data from a benchmarking audit suggests that Infectious Diseases Acute Physician (IDP) management was associated with approximately 30% less total antibiotic use in acute medical admissions compared to other Acute Physicians, with fewer patients being given an antibiotic, and shorter courses. Examination of clinical outcome in these audit patients, and in a much larger hospital administrative dataset, suggests this antibiotic reduction was achieved without adverse patient outcome. The reduction in total antimicrobial use by the IDP was not due to differences in antibiotic choice or compliance with guidance. A key contributory factor was reduced antibiotic initiation in stable patients where there was diagnostic uncertainty. However, as a potential unintended consequence, there was an association between IDP management and increased overnight admissions and length-of-stay. In the IDP team the strategy therefore appeared to be 'hold and observe', perhaps where a perceived antibiotic 'safety net' was replaced with one based on observation and greater degree of diagnostic certainty. This was supported by anecdotal feedback from junior physicians, who identified (i) an attitude in the IDP team of 'you must justify why you gave antibiotics' compared to 'give antibiotics, just in case' (as previously

described by others[181]), (ii) the use of antibiotics to 'give a diagnosis' in cases of uncertainty, and (iii) the view that antibiotics are often used as a 'safety net' where there is pressure from patients, healthcare targets[182] or limited bed availability to avoid admission. A fuller qualitative methods study would have been valuable in further exploring this issue, and this was discussed with my supervisors. Ultimately it was felt that the focus of the thesis was to build research experience and progress knowledge using electronic health record data. However this remains an interesting avenue of future investigation. Although full investigation of these factors was outside the remit of this study, it reinforces the importance of the complex decision making process and social factors on antibiotic prescribing[172]. Increased admissions may also reflect a tendency of the IDP to pursue greater diagnostic precision for infection diagnoses, as previously noted by Borer et al[170]. Alternatively physicians trained in other specialties such as elderly care may have more experience with community care resources, enabling prompt discharge of the predominantly older medical population. However, this would not explain the discrepancy in antibiotic use since antibiotic treatment after discharge was taken into account when determining DOT.

2.4.2 **Study strengths and limitations**

Study strengths include the 'real-life' clinical relevance of the study population and multivariable analysis of patient-level data to study prescribing and clinical outcome. I performed a robust risk-adjusted multivariable analysis of prescribing to show differences in antibiotic use are not an artefact of case mix. I also conducted an analysis of clinical outcome both in the smaller 1 week study and a much larger 3 year study of electronic health record data to increase my power to investigate associations with mortality.

Limitations include the restricted audit size, which was also smaller than planned. Whilst I was able to subsequently examine a larger administrative dataset with similar patient characteristics to assess outcome, individual level prescribing and clinical data was not available in this larger dataset, requiring extrapolation that IDP and non-IDP antibiotic use would have been similar over the longer period of time. During the audit, data collection was by a single clinician unblinded to management team, with possibility of recording bias for clinical factors, although objective criteria were used wherever possible. Although acute physicians were made aware of the audit and the exact date was not announced, the IDP may have been more aware of the monitoring due to closer professional relationships with myself, and larger differences in prescribing found due to extra attention on antibiotic use in the IDP team. The study focused on one IDP; whilst IDPs with similar training and integration to acute medicine exist around the UK, replicating the findings with more IDPs at different locations is required before these findings can be generalised to IDPs as a group.

Whilst the study was conducted on patients admitted during an unselected medical take, it is possible that the acute physician's speciality may have led to a difference in patients referred to the acute medical service. For instance, the emergency department physicians may have referred more patients with routine infections because they knew that they would get a specialist infection opinion. (The general practitioners referring patients however would usually be unaware of the acute physician's speciality.) However, this would be expected to lead to increased overall antibiotic use in the IDP patients, rather than reduced use.

It is also possible that the IDP-led team may have different behaviour in recording information in the medical notes, which were subsequently used to classify the diagnoses. For instance, they may feel that higher thresholds of proof are required to diagnose an infection; whilst other physicians may consider a positive urine dipstick in a confused individual enough to diagnose a UTI, the IDP-led team may document this as 'delirium possible UTI or

other cause'. It is unclear what effect this might have on the analysis. If this were the case though, one would expect to see a higher percentage of patients seen by the IDP team classified as 'medium likelihood' infection, and a correspondingly lower percentage classified as 'high likelihood' of infection. This was not observed, with percentages being extremely similar between IDP and non-IDP teams.

The study was single-centre; understanding generalizability to other centres remains important. Cost impact has not been assessed, though I note that as overnight stays currently cost over £250[183], even small increases in admissions will likely dwarf modest antibiotic cost savings. My evaluation did not challenge the validity of the documented working diagnosis, which may have been influenced by preferred antibiotic choice. Judgements on appropriateness can differ substantially depending on the assessor[184]; the resource requirements for robust assessment were outside those available for this study. Future work should include investigating whether the relationship between reduced antibiotic use and more admissions is seen in multiple different healthcare settings, and use of newly-available larger hospital datasets with electronic prescribing to further elucidate patient and procedural consequences of changes in prescribing strategies.

Finally, much larger studies are required to examine the link between these prescribing strategies and subsequent risk of resistant infection. Given the relatively rare outcome of resistant infection, at least in the UK setting[66], it would require an extremely large randomised controlled trial to meaningfully assess the impact of an intervention on resistance. A more realistic way of achieving this is likely to come through the use of electronic health record data analyses. In this study it was only possible to assess mortality and length of stay data using administrative health record data. Linking prescribing and microbiological data would allow these analyses to be performed on a large scale without the

need for the resources of conducting a trial, though use of this data comes with its own limitations.

2.4.3 **Comparison to previous studies**

My findings confirm those of other studies of the potential for antibiotic use reduction in the acute mixed-case setting. A study of 129 adult patients admitted to a US tertiary hospital found 30% of total antimicrobial days were judged unnecessary by study investigators[65] but there was no intervention to treat patients with this reduced amount. Another interventional study found that implementing a post-prescription review in 5 US academic tertiary care centres and 2428 acute hospital patients led to 7% and 16% reductions in antibiotic use at two sites with established stewardship programmes, respectively, but no reduction at the other three sites[178]. This study did not include antibiotics prescribed for use after discharge, and did not examine clinical outcomes. Analysis of antibiotic use in a risk-adjusted analysis in 103 US academic medical centres at an institutional level showed significant inter-hospital variability in expected antibiotic use[175].

Similar to previous studies, I found IDP input associated with a reduction in antibiotic use[168,171]. However the increased length of stay I observed is contrary to Borer et al who found IDP management was associated with shorter lengths of stay[171]. This study retrospectively assessed management of patients diagnosed with infections, and thus may not have captured management decisions made with acute patients of uncertain diagnosis, which is where I saw the 'admit and observe' behaviour which was likely contributory to my IDP-associated longer lengths of stay.

2.4.4 **What this study adds**

My study adds to this body of work by demonstrating reduced antibiotic prescribing using patient-level data to adjust for case-mix and conducting a robust analysis of clinical outcome data to assess patient safety, providing further evidence of the potential for safe antibiotic reduction. It also examines for the first time the effects of IDP management in patients at presentation, rather than after a period of assessment and provisional diagnosis of infection being made. It reports an association with reduced antibiotic use and increased admissions in the acute setting, contrary to previous studies[165,171].

2.4.5 **Implications for clinical practice**

This study suggests that there is the potential to significantly reduce antimicrobial prescribing, and patients exposed, in the acute setting, but highlights that overzealous attempts to focus solely on this to the exclusion of other factors may have unintended consequences, as physicians may employ compensatory changes in patient management to maintain an acceptable 'safety net' in cases of clinical uncertainty.

It is interesting to compare the strategy apparently used by the IDP of 'hold and observe' to the 'delayed prescribing' strategies that have been evaluated for antibiotics in respiratory tract infections in primary care[185]. As covered in Chapter 1, a concern about implementing these in secondary care is the higher likelihood of severe infections and greater potential risk if left untreated. The 'hold and observe' strategy appeared to only have been implemented in the patients where there was true diagnostic uncertainty and where there was no evidence of sepsis or immunosuppression – one may consider this is effectively excluding those at high risk of deterioration if left untreated. It is worth considering further work to explore whether it is possible to identify subgroups of patients who may benefit from a 'hold and observe' policy. An obvious group are the older patients with acute functional decline, but without

clear evidence of infection, who are going to be admitted to the hospital anyway due to care issues, thus minimising the resource cost of an extra period of observation.

2.4.6 **Conclusions for this study**

In conclusion, my study provides further support that antibiotic reduction can be achieved safely in the acute setting, but at the expense of more, and longer admissions. This could be done by replacing a perceived 'antibiotic safety net' ('prescribe and discharge') with one based on observation and greater degree of diagnostic certainty ('hold and observe'). Whilst the findings require replication in other healthcare settings, they suggest that attempts to reduce antibiotic use may come at the expense of increasing admissions and exposure to the hospital environment; this may increase both costs to healthcare services and the burden on already-stretched acute services. Given that admission to hospital is a risk factor for resistant infection, it may also conversely increase the spread of resistance[186]. Ultimately whilst this study supports the potential to reduce antibiotic use, it also highlights the need for larger studies, and the robust assessment of potential 'unintended consequences' of antibiotic reduction policies, and their effect on not just prescribing, but also clinical outcome, resource impacts, and ultimately, risk of resistant infection.

3 CHAPTER 3: TO WHAT DEGREE CAN CHARLSON COMORBIDITIES ASSESSED USING DISCHARGE-ASSIGNED DIAGNOSTIC CODES BE USED TO ASSESS COMORBID STATUS AT ADMISSION FOR USE IN ELECTRONIC HEALTH RECORD STUDIES?

3.1 INTRODUCTION

3.1.1 The relevance of assessing coding-based estimations of Charlson comorbidities

In Chapter 2, I identified that studies analysing the effects of antibiotics using clinician-collected data within the resources of my D.Phil. (hundreds, rather than thousands of patients) lacked power to meaningfully assess clinical outcome, which is crucial for investigating whether particular antibiotic strategies are associated with beneficial or adverse overall clinical outcome – in particular mortality, readmissions, and complications.

One method of addressing this is to conduct much larger studies using routinely-collected electronic health record data, which I also performed to a limited degree in Chapter 1, comparing 3 years of data on clinical outcome between a physician who used less antibiotics and their colleagues. This routinely-collected data enables large study sizes without the significant resources of collecting the data.

A key need in conducting studies of antibiotic use in patients admitted to hospital is to be able to adjust for case mix. Variables such as age and deprivation index (based on postcode) are relatively straightforward to measure using routinely collected data. Comorbid status can be measured, but relies on the analysis of the diagnostic codes that the clinical coding team assign to admission episodes, and using these to estimate the presence or absence of key comorbidities.

It is important to acknowledge that the clinical coding process is largely carried out to record hospital activity for purposes of reimbursement. In employing sound principles of data science, there needs to be a clear understanding of the limitations of any data used. The use of this coded data has expanded far beyond its original remit for activity recording and reimbursement. As well as research/big data studies, it is being used to evaluate hospital performance in standardised hospital mortality indexes[189,190], and has been proposed for use in disease surveillance[191]. Given that these measures are increasingly being linked to significant consequences for reporting organisations, such as funding, penalties, extra hospital surveillance and prestige[10], there are significant pressures on the system which may inadvertently encourage variation in coding behaviour if it may have positive consequence for the organisation[190,192-194]. To try and address coding issues, clinical coding is highly standardised and regularly audited[187,188]. Clinical coders have standardised training and extensive, national-and-international guidance documents[195,196], as well as close overview, which in the UK is performed by the Health and Social Care Information Centre, now known as NHS Digital. In the future it may be possible for alternative methods of data capture to be used, based on natural language processing and/or machine learning from what is documented on electronic records[197,198].

In the following two Chapters, I will seek to better understand the ways that diagnostic codes assigned to an admission relate to clinical diagnoses, in order to quantify their accuracy and limitations, to inform my subsequent study design to investigate the association between antibiotic use and risk of antibiotic-resistant infections. In this Chapter, I will assess to what degree diagnostic codes can represent the comorbid state of a patient at point of admission, and can be used in risk-adjusted models. In the subsequent Chapter I will assess to what degree diagnostic codes can be used to represent clinical diagnoses of infection.

3.1.2 Previous studies of the accuracy of coding-based Charlson comorbidity estimation

Somewhat surprisingly, the accuracy of diagnostic codes with regards to clinician-recorded presence of Charlson comorbidities (the standard score that is almost universally used to reflect comorbidity) has had limited assessment, which I have summarised below.

The first widely-accepted study to attempt to estimate comorbidities from diagnostic codes was done by Deyo et al[199] in 1992 using the World Health Organisation ICD-9 codes, estimating the Charlson index in admissions for spinal surgery. They did not investigate the accuracy of codes, but showed that the estimated Charlson index predicted surgical complications and mortality.

This ICD-9 algorithm was adapted subsequently by Sundararajan et al in 2004[200] to use the ICD-10 codes that are currently used by UK hospitals. Using this method, they identified a 'basket' of codes which represented the Charlson comorbidities, and a patient was considered to have the comorbidity if there was the presence of any of these codes assigned to the admission. In 2005, Quan et al[201] assessed both the Deyo ICD-9 code 'basket', the Sundararajan ICD-10 basket and other iterations, concluding that the newer ICD-10 algorithms produced similar estimates of comorbidity prevalence, and possibly outperformed ICD-9 algorithms in predicting mortality.

In terms of assessments of the accuracy of Charlson comorbidities, Quan et al[202] studied 1200 admissions in the Calgary region of Canada in 1996. A clinically-qualified chart reviewer spent on average 1 hour per chart reviewing the entirety of the available medical documentation and recorded presence of Charlson comorbidities. This was compared to the Deyo et al ICD-9 estimation of Charlson comorbidities. They found that coding-based estimation had an overall sensitivity of 52% for individual comorbidities ranging from 25% for peripheral vascular disease to 82% for diabetes, with positive predictive value (PPV)

overall of 77%, ranging from 44% for severe liver disease to 96% for cancer. They identified that specificity overall was 99%, with the lowest specificity being 97% for diabetes, highlighting that codes were rarely assigned in the absence of disease. They noted that the clinician spent around an hour reviewing each set of notes, leading to a cost of recording comorbidities for the 1200 patients of approximately $25,000, whilst the coding-based data was essentially free. Similar results were obtained by Humphries et al[203], looking at 1994-5 Canadian data.

A Danish study[204] looked at the degree to which coding-based estimations of Charlson comorbidity matched with presence of the comorbidity as recorded by the treated physician. They studied 950 hospitalisations from 1998-2007, finding the PPV for comorbidities ranged from 82% (diabetes with complications) to 100% (congestive cardiac failure and nine other comorbidities) with overall PPV 98% (95% CI 97-99%). They noted that this PPV was higher than other studies performed in Denmark which studied particular diagnoses using objective criteria, rather than clinician assessment, and this may be a source of discrepancy. They did not perform any in-depth study of the reasons for discrepancies but felt overall that the high PPV supported the use of diagnostic-coding based assessment of comorbidity for case mix adjustment.

A larger Australian study[205] looked at the quality of data recording during the coding process, comparing diagnostic codes assigned by the routine coding process, and those assigned by experienced coders acting as auditors. The looked at audit data for 14,635 admissions over 2 years in a large Australian teaching hospital in the Victoria region. They found good agreement for Charlson codes with weighted Kappa 0.88. However there was no clinician assessment or objective criteria used for the recording of comorbidity in the study.

Different versions of coding algorithms exist for estimating Charlson comorbidities from ICD-10 codes. Sundararajan et al[206] compared three different algorithms using data from four different countries, and found that distribution of comorbidity level categories and mortality prediction was similar for all three. The Sundararajan method has been adopted, with modifications, in the UK for use in standardised hospital mortality assessments[177,207].

3.1.3 **Research questions for this study**

Oxford data specifically has not previously been interrogated, and so I aimed to assess whether it broadly represented previous studies, and also investigate several other issues that may affect the design of my future studies in this thesis.

Previous assessments compared diagnoses upon discharge with diagnostic codes assigned upon discharge. What has not been studied in depth is the degree to which diagnostic codes, which are by necessity assigned at discharge, reflect comorbid status upon admission. As an example of why this may be relevant to studies using risk-adjusted models, consider a previously well patient with no comorbidities presenting to hospital with an infection. Due to inadequate antibiotic treatment they develop septic shock, renal failure, liver failure and have an acute ischaemic myocardial event. The diagnostic codes assigned upon discharge would reflect all of the "conditions that co-exist at the time of admission, that develop subsequently, or that affect the treatment received and/or the length of stay". Thus using diagnostic codes assigned at discharge could run the risk of overestimating pre-illness comorbid state. If an antibiotic treatment were inferior and patients were suffering more in-hospital complications, using diagnostic codes assigned upon discharge runs the potential risk of over-estimating comorbid status of the patient group on inferior treatment, and thus in a risk-adjusted model,

potentially underestimating, or even missing, associations between the inferior treatment and adverse outcome.

Interestingly, in the original Deyo study which looked at admissions for spinal surgery, they deliberately designed their ICD-9 based algorithm such that complications that could plausibly have happened as the result of spinal surgery, such as acute myocardial infarction, were calculated based on prior admissions only, not the admission linked to surgery. This was not subsequently carried over to future algorithms.

The true size of the disparity between admission comorbidity and discharge diagnostic codes has not previously been quantified, and I therefore aimed to assess whether the issue was large, or in fact small enough that it would not significantly impact on my future analyses.

I also aimed to compare the accuracy of Charlson comorbidity estimation using diagnostic codes to my own data collection process. In considering the design of future studies, should comorbidity estimation using diagnostic coding prove to have significant inaccuracies, a key question will be – would clinician data collection be substantially more accurate to justify a much smaller study size?

Finally, understanding the reasons for disparities between coding-based estimation of comorbidities and clinician-assessed admission comorbidity may assist in understanding whether there are systematic issues which may either lead to study bias (e.g. is there under or over-recording of comorbidities?) and allow me to consider strategies to address this in future studies.

The availability of clinician-collected data from my 1 week benchmarking audit of antibiotic use in acute medicine described in Chapter 2 provided me with the opportunity to analyse the relationship between Charlson comorbidities[176] identified from diagnostic codes assigned

upon discharge to a linked admission, comorbidities at admission as recorded by a notes review by a single clinician, and the 'true' comorbidities as assessed by re-review of discrepant cases by the clinician, with guidance from a local coding team.

The research questions I aimed to address are how accurate are Charlson comorbidity estimates, based on diagnostic coding, in terms of accurately measuring comorbidity at time of admission to hospital, and thus can they be used in risk-adjusted models in the Oxfordshire population? Are they more or less accurate than a single clinician review of medical documentation? And are there any patterns of error that may result in bias to a study one way or the other?

3.2 METHODS

3.2.1 Data source

Data from a benchmarking audit of antimicrobial prescribing in medical admissions was used, as described in Chapter 2. Briefly, this was prospective data collection for all acute admissions to the medical service in a UK tertiary care centre (John Radcliffe Hospital, Oxford) from 08:00 16th April–08:00 23rd April 2013. These admissions were then matched to electronic health record data.

3.2.2 Data collected

3.2.2.1 *Charlson comorbidities based on electronic health record data*

The Charlson comorbidities based on coding were calculated using previously reported methods. Of note, this only uses the codes assigned to the 'dominant episode', which is the first episode in the spell, unless this has a primary code which designates a symptom rather than condition (an ICD-10 'R' code), in which case it is the second episode. (If the second episode also has a primary 'R' code, then the dominant episode reverts to the first episode.)

In this study, I did not have access to all the codes assigned to all episodes in the spell, only the codes assigned to the dominant episode.

3.2.2.2 *Initial clinician recording of Charlson comorbidities on admission and discharge*

As part of the original benchmarking audit, I reviewed the categories of Charlson comorbidities and recorded the presence of each comorbidity based on notes review at point of admission, denoted the 'initial clinician assessment'. Comorbidities were judged present if a clinician had recorded them in the notes or if there was sufficient evidence in the notes to make the diagnosis (such as a chronically elevated creatinine indicating renal disease) – objective criteria were not used. Of note, this was not intended or analysed as the gold-standard. The average time for review of one set of notes was around five to ten minutes.

3.2.2.3 *Charlson comorbidities – judging true presence of comorbidity at point of admission*

After the initial data collection phase, presence/absence of comorbidities were compared with matched electronic records, and if discrepant, documentation and notes were re-reviewed, and the reason for the discrepancy recorded. The average time for this re-review was around 10-15 minutes. In case of lack of clarity, the case was discussed with the clinical coding team. 13/131 (10%) sets of discrepant notes from admissions were not available for re-review at this later stage, and were not included in the final analysis. If both hospital and initial clinician assessment were concordant, the assumption was made that this represented true presence/absence. Thus the "gold standard" used in this study is either concordance of clinician and hospital assessment, or if this is absent, a single clinician re-review with coding team input.

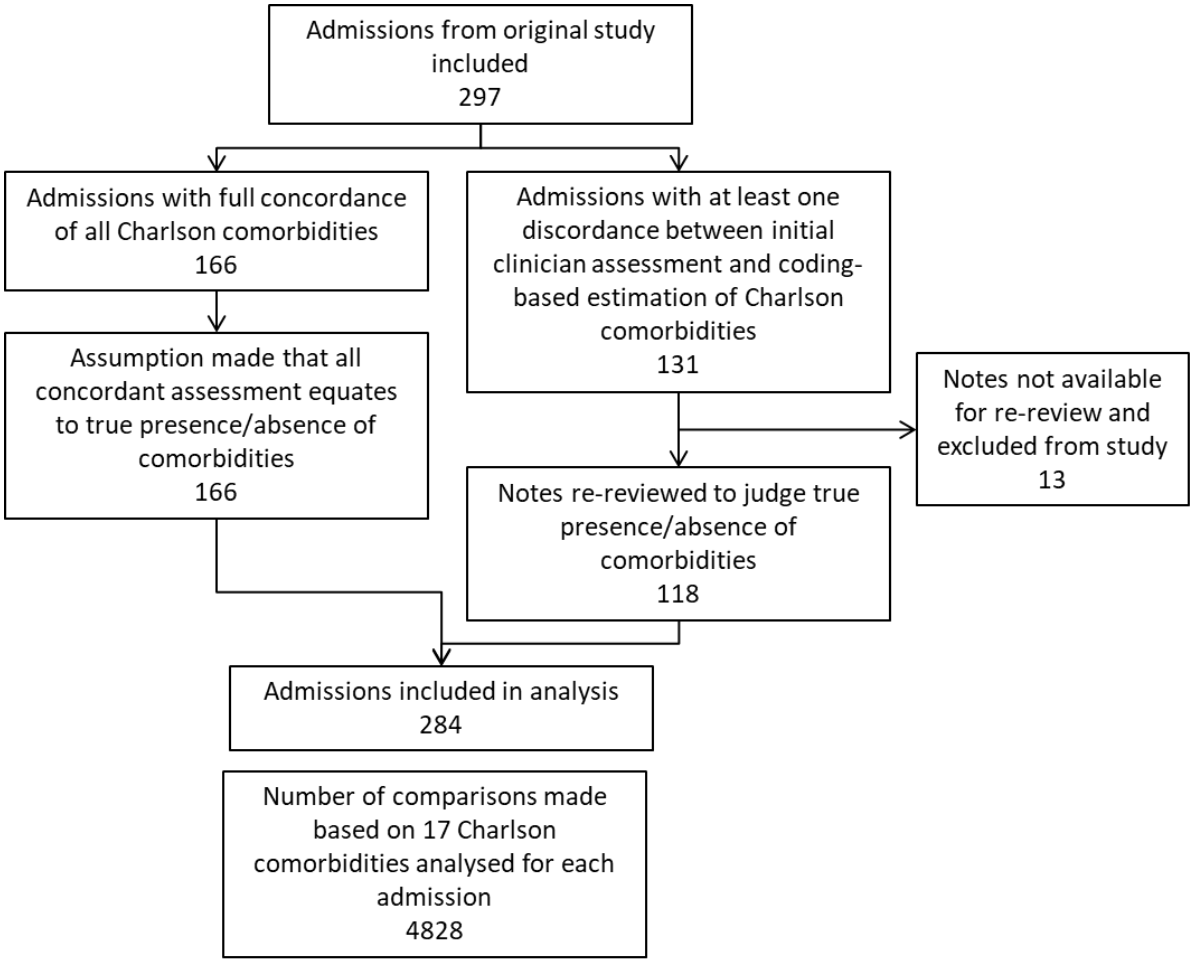


Figure 10: Study protocol and inclusion of admissions in final analysis

3.2.3 Analysing reasons for discrepancies between coding-based estimations, clinician recorded comorbidities and true presence

I reviewed the reasons for the discrepancies identified, and grouped them thematically. In cases where no diagnostic code was recorded by the hospital team yet appeared present in medical documentation, I discussed these with the hospital coding team. When senior members of the coding team assessed the code should have been assigned, this was classified as "hospital missed". When the coding team assessed that there was a valid reason the code was not assigned due to the clear guidance given that only relevant codes should be assigned, this was recorded as "not relevant to admission". Coding guidance is clear that conditions should only be coded if they fulfil the criteria "all conditions that co-exist at the time of admission, that develop subsequently, or that affect the treatment received and/or the length of stay"[195].

3.2.4 Statistical analysis

Sensitivity, specificity, PPV and negative predictive value (NPV) were calculated as percentages and presented to nearest integer value, unless less than one, then presented to one significant figure. Agreement between coding and the true presence of a comorbidity at point of admission, and agreement between single clinician and true presence were assessed using Cohen's kappa coefficient and presented to two decimal places. Analysis was performed using Stata-MP15.

3.3 RESULTS

3.3.1 Predictive value of diagnostic coding based estimation of comorbidity

Diagnostic coding-based assessments of Charlson comorbidities had an overall sensitivity of 83% for predicting admission comorbidities (based on a final "gold standard" assessment), specificity of 100%, PPV of 93% and NPV of 99% (**Table 11**). Against the same "gold

standard," a single-clinician-based assessment had sensitivity 88%, specificity 100%, PPV 95% and NPV 99% (**Table 12**). Both had a kappa of 0.87 compared to true presence/absence of individual comorbidities.

Coding-based estimation had lowest sensitivity for cerebrovascular disease (13/30 instances identified, 43%), diabetes with complications (1/4 instances, 25%) and peptic ulcer disease (2/4, 50%) (**Table 11**). A fuller discussion of reasons for coding discrepancies is included in the next section. Briefly, on discussion with the coding team, it was relatively common for a past stroke to be reasonably be judged not to be relevant to a new admission, with the criteria being "conditions that co-exist at the time of admission, that develop subsequently, or that affect the treatment received and/or the length of stay" as the threshold for coding secondary diagnoses according to UK guidance.

Specificity was high (98-100%) for all comorbidities. PPV for comorbidity presence at point of admission was reasonable for all codes, with the lowest PPV being for congestive cardiac failure (due to five instances where heart failure was diagnosed after admission, and hence present in discharge diagnostic codes but not known to be present at admission) and peptic ulcer disease (again due to four cases where there was a diagnosis after admission, of which three probably represented pre-existing comorbidities and one probably represented a complication of the presenting complaint – a stomach ulcer in the intensive care unit after admission for sepsis, which is a known complication of intensive care treatment).

3.3.2 **Predictive value of initial clinician-based recording of comorbidity**

Initial clinician-based assessment had lowest sensitivity for paraplegia (4/5 instances identified, 80%) and liver disease (2/3 instances identified 67%) (**Table 12**), both due to relatively rare conditions and the clinician assessment missing the diagnosis. Specificity was

high (98-100%) for all comorbidities. PPV was lowest for metastatic cancer (5/14 (64%) represented true instances) due to the clinician classifying haematological malignancy (such as lymphoma) as metastatic cancer, whilst the original Charlson classification considers it cancer (not metastatic)[176], and diabetes with complications (4/5 (80%) represented true instances) due to the clinician assessment considering peripheral vascular disease a complication of diabetes, which the original Charlson classification does not.

Table 11: Accuracy of Diagnostic coding-based prediction of admission Charlson comorbidities

			Present		Absent						
	Present	Absent	True +	False -	True -	False +	Sensitivity	Specificity	PPV	NPV	kappa
acute MI	28	256	28	0	255	1	100	100	97	100	0.98
cancer	22	262	16	6	260	2	73	99	89	98	0.79
cerebrovascular disease	30	254	13	17	254	0	43	100	100	94	0.58
congestive heart failure	24	260	21	3	255	5	88	98	81	99	0.82
pulmonary disease	71	213	68	3	212	1	96	100	99	99	0.96
dementia	20	264	20	0	263	1	100	100	95	100	0.97
diabetes complications	4	280	1	3	280	0	25	100	100	99	0.40
diabetes	49	235	46	3	233	2	94	99	96	99	0.94
paraplegia	5	279	5	0	279	0	100	100	100	100	1.00
HIV	0	284	0	0	284	0	-	100	-	100	0.00
metastatic cancer	9	275	7	2	275	0	78	100	100	99	0.87
liver disease	3	281	3	0	280	1	100	100	75	100	0.86
peptic ulcer disease	4	280	2	2	276	4	50	99	33	99	0.39
peripheral vascular disease	13	271	10	3	270	1	77	100	91	99	0.83
renal disease	30	254	23	7	251	3	77	99	88	97	0.80
connective tissue disorder	17	267	11	6	267	0	65	100	100	98	0.78
severe liver disease	1	283	1	0	283	0	100	100	100	100	1.00
all	330	4498	275	55	4477	21	83	100	93	99	0.87

Table 12: Accuracy of single clinician-based prediction of admission Charlson comorbidities

			Present		Absent						
	Present	Absent	True +	False -	True -	False +	Sensitivity	Specificity	PPV	NPV	kappa
acute MI	28	256	27	1	256	0	96	100	100	100	0.98
cancer	22	262	20	2	261	1	91	100	95	99	0.92
cerebrovascular disease	30	254	24	6	254	0	80	100	100	98	0.88
congestive heart failure	24	260	20	4	260	0	83	100	100	98	0.90
pulmonary disease	71	213	64	7	208	5	90	98	93	97	0.89
dementia	20	264	18	2	264	0	90	100	100	99	0.94
diabetes complications	4	280	4	0	279	1	100	100	80	100	0.89
diabetes	49	235	44	5	235	0	90	100	100	98	0.94
paraplegia	5	279	4	1	279	0	80	100	100	100	0.89
HIV	0	284	0	0	284	0	-	100	-	100	-
metastatic cancer	9	275	9	0	270	5	100	98	64	100	0.77
liver disease	3	281	2	1	281	0	67	100	100	100	0.80
peptic ulcer disease	4	280	4	0	280	0	100	100	100	100	1.00
peripheral vascular disease	13	271	10	3	271	0	77	100	100	99	0.86
renal disease	30	254	23	7	254	0	77	100	100	97	0.85
connective tissue disorder	17	267	16	1	265	2	94	99	89	100	0.91
severe liver disease	1	283	0	1	283	0	0	100	-	100	0.00
all	330	4498	289	41	4484	14	88	100	95	99	0.87

Table 13: Reasons for discrepancies in single clinician-based prediction of admission Charlson comorbidities

	cause	number	% total assessments	% of total errors	grouped % of total errors
Reasons for discrepancies					
Hospital Error	Hospital missed	24	0.5	18	22
	Hospital misinterpreted clinical notes	5	0.1	4	
Clinician Error	Clinician missed	35	0.7	27	42
	Clinician misinterpreted coding	20	0.4	15	
Correct coding process does not represent admission diagnosis	Ambiguous documentation	5	0.1	4	34
	Diagnosis not relevant to admission	26	0.5	20	
	In-hospital diagnosis, complication	2	0.04	2	
	In-hospital diagnosis, pre-existing	14	0.3	11	
Correct percentages/totals					
Clinician called correct presence/absence of admission comorbidity		4773	98		
Coding called correct presence/absence of admission comorbidity		4752	98		
Coding and clinician called correct presence/absence of admission comorbidity		4699	97		
Total		4828	100		

3.3.3 **Reasons a code was not assigned in the presence of comorbidity**

In a total of 55 instances a code was not assigned by the hospital coding team despite the judged presence of comorbidity at point of admission on re-review of the notes (see **Table 11**) total false negative instances).

In 24 instances, a diagnostic code was not present when a relevant comorbidity was clearly documented and felt relevant to the admission (denoted 'hospital missed' in **Table 13**). There was no clear pattern, with a fairly even distribution of comorbidities involved, and no recurring/systematic errors identified. For instance, a patient admitted with pulmonary oedema did not have congestive cardiac failure coded, and a patient admitted after recurrent falls had ongoing chemotherapy for breast cancer, which the coding team assessed should have been coded as she was on active treatment and the cancer would have contributed to her weakness. Some of the cases were slightly ambiguous – such as a patient admitted with delirium secondary to pneumonia who had had a previous large stroke – on balance it was felt that a patient with a previous stroke was going to be more prone to future delirium, and whilst they could have coded it, they understood why it may not have been judged 'relevant to the admission', also highlighting the subjective nature of this judgement, and that it can be influenced by the experience of the coder.

In five instances (Table 13, denoted 'ambiguous documentation'), a diagnostic code was not assigned for reasons considered related to ambiguous documentation. In four cases, this was due to a clinician recognising patterns of high creatinine in the past being consistent with chronic kidney disease, but this not being documented specifically in the medical notes, meaning that renal disease was not coded. In one case, the clinician could recognise the pattern of disease and investigations represented a diabetic nephropathy, so assigned the Charlson comorbidity of 'diabetes with complications', but as this condition was not clearly documented in the notes, the coding team would have been unable to assign it.

In 26 instances, a code was not assigned because the coding team felt it probably was not relevant to the admission (**Table 13**, 'diagnosis not relevant'). 15 of these were due to a prior stroke not being coded, for instance in patients presenting with a rash due to eczema, chest pain, or an infection of the foot. In a few of these cases, the decision was ambiguous, such as the patient presenting with falls due to low blood pressure, where a clinician may see that antihypertensive medication (which is often started after strokes as secondary prevention) may have contributed, but on balance the coding team felt there was valid justification for not coding the stroke. In three cases cancer was not coded as the patient had had cancer treated to remission previously, and the presentation was not relevant to past cancer diagnosis or treatment. The remaining instances – two pulmonary disease, three peripheral vascular disease, one renal disease and one connective tissue disease – were all comorbidities felt not relevant to the admission, like a patient with leg swelling with a possible deep vein thrombosis and a previous diagnosis of rheumatoid arthritis not currently on treatment. Again, on discussion, a clinician might justify that patients with rheumatoid arthritis are at increased risk of a deep vein thrombosis due to an increased inflammatory response and possible decreased mobility, but the coding team highlighted that coders are not clinically trained and following their training, this would have been a reasonable comorbidity to judge not relevant.

3.3.4 Reasons a code was assigned in the absence of comorbidity at point of admission

In 21 instances, a code was assigned despite the comorbidity being absent at point of admission (false positive number in **Table 11**).

In five instances a comorbidity was coded by the hospital when not present(**Table 13** denoted 'hospital misinterpreted clinical notes'). Two patients with acute renal failure were coded as

chronic kidney disease despite previously normal renal function. A breast cancer patient was admitted with hypercalcaemia (cancer not relevant), a dementia code was recorded for one patient despite only possible dementia being recorded in notes, and a ductal-carcinoma in situ (DCIS) was given a breast cancer code, despite a DCIS having a separate code which does not contribute to the Charlson 'code basket'.

In 16 instances the discrepancy was due to a new diagnosis being made in-hospital. However, it was only in two cases that these represented sequelae of the cause for admission. In one, this was an in-hospital heart attack secondary to sepsis. In another, a patient developed a gastric ulcer in the intensive care unit during treatment for sepsis – a recognised complication of intensive care treatment.

In all other 14 cases, these in-hospital diagnoses were due to a comorbidity that was present but undiagnosed at point of admission. There was one new identification of peripheral vascular disease in a patient with a foot ulcer. There were two new diagnoses of duodenal ulcers as a cause for vomiting and one new diagnosis of gastric ulcers in patient presenting with a diabetic ketoacidosis due to vomiting precipitated by the ulcer (again all suggesting pre-admission comorbidity). There was one new diagnosis of alcohol-induced liver cirrhosis in a patient presenting with a gastrointestinal bleed. There were two new diagnoses of type 1 diabetes in patients presenting feeling unwell, one brain tumour diagnosed as the cause of right-sided weakness, one new diagnosis of asthma in a patient with shortness of breath, and five new diagnoses of heart failure in patient presenting with breathing issues.

3.3.5 **Reasons why a clinician did not record a comorbidity when it was present**

In 41 instances, I did not record the presence of a Charlson comorbidity on initial assessment, despite it being evident at point of admission on subsequent re-review of the notes (false negatives, **Table 12**)

In 35 instances (denoted "clinician missed" in **Table 13**), this was due to a simple omission or error. For instance, a patient who clearly had chronic kidney disease documented, I did not record.

In six instances (denoted "clinician misinterpreted coding" in **Table 13**), I did not record the presence of a Charlson comorbidity because of an incomplete understanding of the comorbidities included in the Charlson 'basket'. Specifically, I did not include bronchitis as a respiratory disease, a renal transplant as chronic kidney disease, polycystic kidney disease as chronic kidney disease, carotid stenosis as peripheral vascular disease, and in two cases, a vascular graft as peripheral vascular disease.

3.3.6 **Reasons why a clinician recorded a comorbidity when it was not present**

In 14 instances, I recorded the presence of a Charlson comorbidity despite the absence of this comorbidity at point of admission (false positives, **Table 12**)

This was mainly due to a misunderstanding or mismatch of what conditions legitimately contribute to the Charlson (hence also denoted "clinician misinterpreted coding" in **Table 13**). The most common causes of this clinician-based error was recording haematological cancer as metastatic cancer (five instances), when the Charlson basket has it as non-metastatic cancer. Similarly, I classified five instances of interstitial lung disease or pulmonary aspergillosis as pulmonary disease. I have classified this as a clinician error as interstitial lung disease codes are not in the Charlson 'basket' of codes used by Sundarajan et

al[200]. On review of the 'original' Charlson publication[176], lung disease was classified according to the degree of dyspnoea or oxygen requirement. As such, one could alternatively call these five instances 'limitations of the Charlson coding basket'. Similarly, I classified one case of granulomatous polyangiitis (GPA) of the kidneys as chronic kidney disease although the code for this does not form part of the basket. Although GPA is commonly thought of as a cause of acute, rather than chronic kidney disease, a prior history will often leave the patient with chronic renal impairment, though in this case the patient had normal renal function. I classified a psoriatic arthritis as connective tissue disease although this was not included in the original classification, and peripheral vascular disease as a complication of diabetes. Whilst one can argue that patients with diabetes are at increased risk of peripheral vascular disease, this is not recognised by the Sundararajan et al classification and was not included in the original Charlson classification.

3.4 DISCUSSION

3.4.1 Major findings

In the vast majority of cases, the diagnostic codes accurately represented comorbidities of the patient at point of admission. The recording of comorbidities by a single clinician in around 10-15 minutes of notes review was not substantially more accurate than diagnostic coding-based estimation of comorbidities.

The only condition that was relatively frequent and significantly under-recorded was cerebrovascular disease, where only 13/30 instances were identified by coding, which the clinical coding team felt was likely because it was not judged to be relevant to the admission. However, they acknowledged that the threshold for relevance was subjective and dependent on a coder's own experience, and a potential weakness of the UK guidance to only code

relevant codes. This highlights the UK prioritisation that the primary aim of coding is to match reimbursement with the likely complexity of the treatment needed for the patient, and try and avoid 'coding inflation' or 'upcoding' practices[192,194] – where many codes are assigned that may be irrelevant, but boost the amount of money that the trust receives for care of the patient. This prioritisation practice may improve valid reimbursement and avoid overpayment, but may affect data quality by reducing sensitivity of coding-based assessments of disease incidence. The overall contribution of this under-recording was, however, small overall.

Specifically in the study of infectious diseases, practices like coding inflation are more likely to cause alterations in the allocation of secondary codes; if coding depth has increased in recent years as a result of financial incentivisation, this may increase the use of secondary 'organism codes' and an artefactual increase in apparent infections due to specific organisms. With regards 'upcoding' and using the highest-tariff code, it is possible that an artefactual increase in codes for more severe infections (such as sepsis) may be seen as a consequence.

Other coding systems than ICD-10 exist, such as MedDRA, and SNOMED-CT. Currently MedDRA coding, developed to facilitate sharing of regulatory information for medicinal products internationally, is not routinely collected in NHS hospitals. SNOMED-CT is used for emergency departments, but not for inpatient hospital medicine.

The number of discrepancies caused by the later development of complications of treatment were numerically tiny - only two new comorbidities arose in 284 admissions as a direct sequelae of the admitting issue (0.7%). When there was a new in-hospital diagnosis, this generally represented an undiagnosed issue that was likely present at point of admission and would have contributed to the overall comorbid status of the patient – in this way using

diagnoses made in hospital could arguably be considered a better representation of the patient's risk of mortality or complications than only the diagnoses at point of admission.

3.4.2 **Strengths and limitations**

This study benefits from in-depth analysis of the reasons for discrepancies between coding-based estimations, initial clinician recording, and true presence of comorbidities, rather than simply reporting statistics. It is conducted on a dataset that is highly relevant to my research aim – Oxfordshire hospitals - given that the future studies this piece of work informs will be conducted on this dataset. It also studies a previously-unaddressed question – the degree to which in-hospital diagnoses may potentially lead to over-estimation of comorbid status at point of admission.

However, this relatively small study has a number of significant limitations that mean its relevance outside this thesis is limited; its purpose was primarily to better understand the Oxfordshire dataset and inform my future study design, and conduct a small validation study for the work in Chapter 1, rather than perform a comprehensive analysis of the accuracy of coding-based assessments of comorbidity, as have been done previously.

A key study limitation is the use of a single clinician to assess the 'true' presence of comorbidity, albeit with input from the coding team. Two clinicians with a third 'tie-breaking' in case of disagreement is preferred and more commonly used, and it is important to highlight this and avoid implying that the error rate of my single clinician assessment represents the error rate of more carefully conducted clinical assessments. In addition, I did not assess the performance of other clinicians – it may be that my performance is substantially different to other clinicians and extrapolating my performance to that of another clinicians is erroneous.

Further, 10% of notes where there was a discrepancy were not available for re-review, so errors rates inevitably have a small degree of downward bias. In the Quan et al study[202], which interestingly also used a single review of notes, they considered the average time to review one set of notes was over an hour. I did not spend this amount of time, even with the re-reviews if discrepant, and it is possible that I may have missed information. Using the same clinician to assess the 'true' presence of comorbidity as had initially performed the assessment is also a significant limitation - it is possible that in assessing true presence there were errors I was unaware of; using another clinician may have picked these up. The above limitations would potentially have led to under-recording of true comorbid status, and a slight over-estimation of the sensitivity of coding-based estimations.

I did not review any concordant assessments of comorbidity. It is possible, indeed likely, that in a few of these cases, both clinician and coding made an error in the recording of a comorbidity, and the true error rate of both of these may be higher than assessed using this method.

I did not have information about the coding from all hospital episodes that form the admission. As per accepted methods, only one episode from the admission has the coding analysed to calculate co-morbidities – this is usually the first hospital episode (or if the first episode is a nonspecific symptom 'R' code, the second episode, unless this second episode also has a primary diagnosis 'R' code). It would be desirable to look at whether any missing codes might be present in other hospital episodes, to consider whether alternative methods, such as using all the codes assigned to all episodes of the admission, may have better predictive ability.

I did not judge presence of comorbidities based on objective criteria, which may have improved true diagnostic accuracy, but in a retrospective review of notes, finding the data to justify objective criteria is often difficult or impossible.

3.4.3 **Comparison to other studies**

This study suggests that coding-based estimations of Charlson comorbidities in the 2013 Oxfordshire dataset have better overall performance than previous assessments of data in Canada 1996 (which had overall sensitivity 52% and PPV 77%, compared to 83% and 93%, respectively, in this study), but worse PPV than a study of Danish data 1998-2007 (PPV 98% compared to 93% in this study). One possible explanation is that the majority of this Danish data was collected before the introduction of widespread activity-based payment (which was less than 15% of total costs in 2005[208]), thus there may have been less focus on minimising 'upcoding' practices. Conversely one could argue a lack of activity-based payment to mean a lack of incentive to encourage coding of multiple comorbidities, thus this explanation is highly speculative.

3.4.4 **Study implications**

Given that coding-based data is essentially time-and-resource-free, use of smaller datasets with clinician review to record comorbidities for the purpose of risk-adjustment for clinical outcomes, cannot easily be justified, especially in the study of relatively rare outcomes where large numbers are a priority. If studies depend on very high accuracy of comorbidity recording, then substantial resources are likely to be needed for clinician review, at around 30-60 minutes of notes review per case.

The finding that some conditions such as cerebrovascular disease may be under-recorded due to a previous stroke being judged not 'relevant to the admission', though numerically small

compared to the total number of comorbidities assessed overall, suggest that, whilst large studies using coding to risk-adjust may be minimally effected, studies investigating the incidence or prevalence of cerebrovascular disease may be affected much more substantially, and careful consideration of study design would be required.

Finally, my concern that using discharge diagnoses to represent admission comorbidity may lead to confounding due to coding of complications of the reason for admission seem largely unfounded, as the coding of these complications was incredibly rare, with only 2 instances in 284 admissions (0.7%).

3.5 CONCLUSIONS

Discharge coding-based estimations of Charlson comorbidities at the point of admission in an Oxfordshire dataset of 284 medical admissions in 2013 had good predictive value for true presence of comorbidities, and performed similarly to a single clinician-based assessment.

4 CHAPTER 4: 'CAVEAT EMPTOR': THE CAUTIONARY TALE OF ENDOCARDITIS AND THE POTENTIAL PITFALLS OF CLINICAL CODING DATA: AN ELECTRONIC HEALTH RECORDS STUDY

4.1 BACKGROUND

4.1.1 Rationale for this study

Electronic health records are a powerful resource, enabling large observational analyses to be undertaken to assess disease outcomes, monitor trends, and assess the effectiveness of healthcare. Their routine collection means that their use in research does not place an additional data collection burden on NHS staff. Identification of diseases in health records is

frequently based on analysis of the World Health Organisation ICD-10[196] diagnostic codes assigned to a patient's hospital admission. Whilst the process of recording these codes upon discharge is internationally standardised and audited, these codes are recorded principally for reimbursement and administration, and multiple sources of potential error exist in the process of assigning codes[192,209]. Previous studies have shown how coded data can create artefactual patterns in mortality[210].

Endocarditis is a useful and clinically relevant 'test case' for studying electronic health record accuracy. It benefits from having objective clinical criteria for defining true diagnoses and shares little overlap with other conditions. Additionally, the low overall incidence of infective endocarditis, even in high-risk populations, means that very large-scale and resource–intensive individually randomised controlled trials would be required to test the benefits of preventative interventions. Thus, electronic health record studies have been particularly important in guiding the management of infective endocarditis.

The importance of understanding the relationship between diagnostic codes and clinical cases goes beyond studies of endocarditis. There is rapidly increasing use of electronic health record data for purposes of research[211-213] and evaluation of hospital performance[177], among a myriad of other uses. Relevant to this thesis (and as discussed in Chapter 2), the relative rarity of resistant infection as an outcome necessitates the conduct of larger studies to meaningfully assess the effect of antibiotic prescribing on resistance. Understanding the degree to which diagnostic codes can be used to estimate the presence of an infectious disease, or particular infective organism, is of crucial importance in informing future study design in this area.

4.1.2 Previous Electronic Health Record studies of endocarditis

Numerous studies have been performed worldwide to assess the impact of changes to recommendations on the use of antibiotic prophylaxis for dental procedures to prevent

infective endocarditis[214-219], with a lack of clear consensus[220-232]. The ICD-10 codes used in available studies of endocarditis are summarised in Table 14. The studies are summarised in **Table 16** and **Table 17** below.

Table 14 ICD-10 endocarditis codes and corresponding ICD-9 codes used in previous studies

ICD-10 Code	Description	Corresponding ICD-9/ICD-9-CM code	Description
Included			
I33 (I330)	Acute and subacute infective endocarditis	4210	Acute and subacute infective endocarditis
I38 (I38.X)	Endocarditis, valve unspecified	4249 42499	Endocarditis valve unspecified cause Other endocarditis valve unspecified
I339	Acute and subacute endocarditis, unspecified	4219	Acute endocarditis unspecified
T826	Infection and inflammatory reaction due to cardiac valve prosthesis	99661	Infection and inflammatory reaction due to cardiac device implant and graft
B376	Candidal endocarditis	11281	Candidal endocarditis
I39 (I390)	Endocarditis and heart valve disorders in diseases classified elsewhere	11504 11514 11594 4211 42491	Histoplasma capsulatum endocarditis Histoplasma duboisii endocarditis Histoplasmosis endocarditis Acute and subacute infective endocarditis in diseases classified elsewhere Endocarditis in diseases classified elsewhere
I398	Endocarditis, valve unspecified, in diseases classified elsewhere		
Not included			

ICD-10 Code	Description	Corresponding ICD-9/ICD-9-CM code	Description
I423	Endomyocardial (eosinophilic) disease	4250	Endomyocardial fibrosis
I091	Rheumatic diseases of the endocardium, valve unspecified	3979	Rheumatic diseases of the endocardium valve unspecified
T827*	Infection and inflammatory reaction due to other cardiac and vascular device, implants and grafts	99661 99662	Infection and inflammatory reaction due to cardiac device implant and graft Infection and inflammatory reaction due to vascular device implant and graft
I011	Acute rheumatic endocarditis	3911	Acute rheumatic endocarditis
Codes that feature only US specialised coding guidance (ICD-10-CM 2010)[233], not in UK datasets			
A3951	Meningococcal endocarditis	03642	Meningococcal Endocarditis
A3282	Listerial endocarditis	42491	Endocarditis in diseases classified elsewhere
A5203	Syphilitic endocarditis	42491	Endocarditis in diseases classified elsewhere
B3321	Viral endocarditis	07422	Coxsackie Endocarditis
A5483	Gonococcal heart infection	09884	Gonococcal Endocarditis

* The T827 code ("Infection and inflammatory reaction due to other cardiac and vascular device, implants and grafts") was not selected as a review of the Oxford 2016 audit data suggested it was overwhelmingly used for wound infections after surgery, and the number of admissions with a primary or secondary T827 code was greater than all other endocarditis-coded admissions combined.

Table 15: Secondary/supplementary organism codes used and reviewed

ICD10 CODE	ICD10 DESCRIPTION
MRSA	
U80.1 + OTHER STAPH CODE	METHICILLIN RESISTANT AGENT
STAPHYLOCOCCUS UNSPECIFIED	
A49.0	STAPHYLOCOCCAL INFECTION, UNSPECIFIED SITE
A41.2	SEPSIS DUE TO UNSPECIFIED STAPHYLOCOCCUS
A41.2	SEPSIS DUE TO UNSPECIFIED STAPHYLOCOCCUS
A41.1	SEPSIS DUE TO OTHER SPECIFIED STAPHYLOCOCCUS
B95.8	UNSPECIFIED STAPHYLOCOCCUS AS THE CAUSE OF DISEASES CLASSIFIED ELSEWHERE
B95.7	OTHER STAPHYLOCOCCUS AS THE CAUSE OF DISEASES CLASSIFIED ELSEWHERE
STAPHYLOCOCCUS AUREUS	
A41.0	SEPSIS DUE TO STAPHYLOCOCCUS AUREUS
STREPTOCOCCUS	
B95.5	UNSPECIFIED STREPTOCOCCUS AS THE CAUSE OF DISEASES CLASSIFIED ELSEWHERE
B95.4	OTHER STREPTOCOCCUS AS THE CAUSE OF DISEASES CLASSIFIED ELSEWHERE
A49.1	STREPTOCOCCAL INFECTION, UNSPECIFIED SITE
A40.8	OTHER STREPTOCOCCAL SEPSIS
A40.9	STREPTOCOCCAL SEPSIS, UNSPECIFIED
A40.3	SEPSIS DUE TO STREPTOCOCCUS PNEUMONIAE
B95.5	UNSPECIFIED STREPTOCOCCUS AS THE CAUSE OF DISEASES CLASSIFIED ELSEWHERE
B95.0	STREPTOCOCCUS, GROUP A, AS THE CAUSE OF DISEASES CLASSIFIED ELSEWHERE
B95.1	STREPTOCOCCUS, GROUP B, AS THE CAUSE OF DISEASES

ICD10 CODE	ICD10 DESCRIPTION
	CLASSIFIED ELSEWHERE
B95.4	OTHER STREPTOCOCCUS AS THE CAUSE OF DISEASES CLASSIFIED ELSEWHERE
B95.2*	STREPTOCOCCUS, GROUP D, AS THE CAUSE OF DISEASES CLASSIFIED ELSEWHERE
B95.3	STREPTOCOCCUS PNEUMONIAE AS THE CAUSE OF DISEASES CLASSIFIED ELSEWHERE
A40.0	SEPSIS DUE TO STREPTOCOCCUS, GROUP A
A40.1	SEPSIS DUE TO STREPTOCOCCUS, GROUP B
A40.2	SEPSIS DUE TO STREPTOCOCCUS, GROUP D
A40.3	SEPSIS DUE TO STREPTOCOCCUS, GROUP D
A40.8	OTHER STREPTOCOCCAL SEPSIS
A40.9	STREPTOCOCCAL SEPSIS, UNSPECIFIED
B95.X	STREPTOCOCCUS, STAPHYLOCOCCUS, AND ENTEROCOCCUS AS THE CAUSE OF DISEASES CLASSIFIED ELSEWHERE
Codes that feature only US specialised coding guidance (ICD-10-CM 2010)[233], not in UK datasets	
B9562	METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS INFECTION AS THE CAUSE OF DISEASES CLASSIFIED ELSEWHERE
A4102	SEPSIS DUE TO METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS
Z1611	RESISTANCE TO PENICILLINS
Z1610	RESISTANCE TO UNSPECIFIED BETA LACTAM ANTIBIOTICS
Z1612	EXTENDED SPECTRUM BETA LACTAMASE (ESBL) RESISTANCE
Z1619	RESISTANCE TO OTHER SPECIFIED BETA LACTAM ANTIBIOTICS

ICD10 CODE	ICD10 DESCRIPTION
A4101	SEPSIS DUE TO METHICILLIN SUSCEPTIBLE STAPHYLOCOCCUS AUREUS
B9561	METHICILLIN SUSCEPTIBLE STAPHYLOCOCCUS AUREUS INFECTION AS THE CAUSE OF DISEASES CLASSIFIED ELSEWHERE
B9562	METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS INFECTION AS THE CAUSE OF DISEASES CLASSIFIED ELSEWHERE
A4101	SEPSIS DUE TO METHICILLIN SUSCEPTIBLE STAPHYLOCOCCUS AUREUS
B9561	METHICILLIN SUSCEPTIBLE STAPHYLOCOCCUS AUREUS INFECTION AS THE CAUSE OF DISEASES CLASSIFIED ELSEWHERE

* From 1st April 2016, B952 became: STREPTOCOCCUS, GROUP D, AND ENTEROCOCCUS AS THE CAUSE OF DISEASES CLASSIFIED ELSEWHERE. The ICD-9 system has had Enterococcus as a separate code 041.04, which maps to B95.2. The OUH coding team had received guidance to code Enterococcus as B95.4 – a *Streptococcus* code.

Table 16: Summary of studies of endocarditis incidence or features using electronic health record data or microbiological data, source of information, codes used, methods of deduplication and comparisons of codes and cases

Author and Year	Details	Finding	Case definition and codes used	Deduplication /other	Comparison of codes to true incidence
Assessment of change associated with change in guidelines					
Tubiana[220] 2017	**Timescale:** 2008-2014 **Country:**France	No increased rate of oral streptococcal endocarditis	Individual with valve prosthesis (code Z95.2,	First hospitalization	Refers to Toyoda et al[228] for choice of codes

Author and Year	Details	Finding	Case definition and codes used	Deduplication /other	Comparison of codes to true incidence
	Population: Adults with valve prosthesis **Study design**:nationwide population-based cohort and case crossover study **Data source**:French health insurance and hospital discharge database **Details:** 138 876 individuals, 52281 had invasive dental procedure. 267 infective endocarditis with oral streptococci.	in individuals exposed to invasive dental procedure with or without prophylaxis compared to non-exposed. Exposure to invasive procedure more frequent in case vs control periods 5.1% vs 3.2%.	T82.6, T82.0) Admission with endocarditis primary code I330 I339 Streptococcus codes:: A40.8, A40.9, A49.1, B95.4, B95.5	with infective endocarditis as defined only	used
Bates[221] 2017	**Timescale:** 2003-2014 **Country:** US **Population**: Children <18 years hospitalized with infective endocarditis at 29 centres **Study design**:Interrupted time series analysis **Data source:** paediatric health information system database. **Details:** 841 cases	Interrupted Time Series analysis: increasing trend pre-guideline change, no difference in rate of change post guidelines. Similar analysis in children with congenital heart disease found similar results.	Admission with Primary or Secondary code 4210 Plus antistreptococcal antibiotics >7 days (vancomycin/penicillin/ceftriaxone monotherapy or vanc/gent combi or cef/pen and gent - American Heart Association guidelines) Also considered congenital heart disease,	First (index) hospitalization with infective endocarditis as defined only	No

Author and Year	Details	Finding	Case definition and codes used	Deduplication /other	Comparison of codes to true incidence
			codes listed in reference Jenkins et al[234]		
Bikdeli[222] 2013	**Timescale:** 1999-2009. **Country:** US **Population**: Older adults: >=65 years with principal/secondary diagnosis of endocarditis **Study design**:Mixed effects models **Data source:** National Nationwide Inpatient Sample (NIS) database **Details:** a in 262,658 individuals hospitalized with endocarditis.	Adjusted hospitalisation rate increased 1999-2005, then decreased, with the decline continuing after 2007. No change in adjusted mortality, and trends consistent across subgroups.	Admission with primary or secondary 4210 4211 4219 4249 Excluded if 996.91code used in any position (intracardiac device).	If multiple hospitalisations in given year (18%), then random hospitalization used (patient unit of analysis)	No Discussion references Fedeli[235], Cabell[236], Mendiratta[237], Rogers[238] Day[239]
DeSimone[240] 2012	**Timescale:** 1999-2009 **Country:** US **Population**:All individuals in the Rochester Epidemiology Project of Olmsted County **Study design**:population-based review and poisson regression modelling	Incidence calculated in three 3-year time intervals No change in viridans group Streptococcus incidence in 3 year period post guideline nationally or in smaller subgroup. Overall decline in incidence noted- authors speculate due to declining	All hospital discharges with streptococcal infective endocarditis primary 421.0 plus Streptococcus code: streptococci unspecified: 041.00; and other streptococci: 041.09. Excluded: strep group A: 041.01; strep group B: 041.02;	All hospital discharges No deduplication	No

Author and Year	Details	Finding	Case definition and codes used	Deduplication /other	Comparison of codes to true incidence
	Data source: National NIS database **Details:** a s in . Approx 135,000 hospitalisations Plus a prospective study using Mayo Clinic Endocarditis registry, Viridans-group modified Duke criteria for endocarditis 1999-2010; total 150 cases, of which 22 cases were viridans group Streptococcus	rheumatic heart disease Rate of incidence National 1999-2002: 3.19/100,000 Local 1.7-3.5 cases/100.000.	strep group C: 041.03; enterococcus group D: 041.04; streptococcus group G: 041.05.		
Duval[241] 2012	**Timescale:** 1991, 1998, 2008 **Country:** France **Population**: 3 french regions, 11million inhabitants >19yrs **Study design**: 3 surveys, incidence rate comparison using possion regression **Data source:** population-based surveys **Details:** , 993 cases.	No increase in overall infective endocarditis incidence or in oral Streptococcal infective endocarditis. Increase in Staphylococcal infective endocarditis in patients with native valve disease	Case identified by healthcare professional and reviewed by expert group	All cases as recorded by healthcare professionals	No
Van den Brink[242]	**Timescale:** 2005-2011 **Country:** Netherlands	Increase in cases from 30/100,000 to 63/100,000	Hospitalisation with Netherlands-specific	Not specified – appears first	No

Author and Year	Details	Finding	Case definition and codes used	Deduplication /other	Comparison of codes to true incidence
2017	**Population**:hospitalised patients **Study design**:retrospective trend study, interrupted time series data **Data source:** Netherlands national insurance healthcare database **Details:** a ; 5213 patients hospitalized with endocarditis	before vs after European Society of Cardiology Guideline change; streptococci responsible for 31-53%	endocarditis code for insurance	national hospitalization per patient counted (reference made to avoiding counting twice for transfers)	
Dayer[223] 2015	**Timescale:** 2000-2013 **Country:** England **Population**: hospitalised patients in England **Study design**:interrupted time series analysis **Data source** National Hospital Episode Statistics (HES) database all patients in England. **Details:**	Increase in infective endocarditis cases/month from 2008 when guidelines changed above projected historical trend in both higher and lower risk individuals.	Admission ('superspell'_ with I33 Primary code	Use of superspells (deduplicated for transfers) Exclusion of waiting list cases (based on preliminary analysis)	"Although these data are subject to error, they have been shown, for example, to provide more reliable and complete data capture for vascular surgery than a UK national research database specifically designed for that purpose"
Keller[224] 2017	**Timescale:** 2006-2010 **Country:** Germany **Population**:hospital	Increase in prevalence per 100,000: 9.5-10.6, then larger increase 2011-2014	Admission with I33 code in any position, with additional organism	No mention of deduplication	No

Author and Year	Details	Finding	Case definition and codes used	Deduplication /other	Comparison of codes to true incidence
	patients **Study design**:linear regression analysis before and after guidelines **Data source:** Federal Statistical office of Germany **Details:** 94,364 patients 'Annual number of inpatients diagnosed with infective endocarditis'	11.1-14.4. Increasing prevalence of Streptococcus and Staphylococcus endocarditis, percentage Streptococcus 20.8% Staphylococcus 21.9% Increasing number of valvular surgeries	codes: Streptococcus: B95.0-B95.5 Staphylococcus B95.6-B95.8		
Pant[225] 2015	**Timescale:** 2000-2011 **Country:** US **Population**:hospitalised patients **Study design**:segmented regression analysis **Data source:** Healthcare cost and utilization project using the NIS Database USA **Details:** a . 457,052 hospitalisations	Increase in incidence of hospitalisations 2005-11, from 11/100,000 to 15/100,000. Increase in all causes (Staphyococcal, Streptococcal, gram-negative, fungal, absolute and percentage – likely due to decreasing number of no-secondary-organism code cases). Both Staphylococcal and Streptococcal cases increasing, but rate of increase of Streptococcal more post-guidelines	Hospitalisation with endocarditis code: 4210 (acute and subacute bacterial endocarditis), 4211 (acute and subacute infective endocarditis in diseases classified elsewhere – e.g. Q fever), 4219 (acute endocarditis, unspecified) Also collected data on organism codes: *S. aureus* endocarditis: 03811, 03812, 04111, 04112, 0381, 03810,	All hospitalisations	Note limitations of multiple admissions per patient (NIS data did not allow deduplication by patient) Acknowledge validation study limitation. Quote Fedeli et al[235] pilot study with PPV 81%

Author and Year	Details	Finding	Case definition and codes used	Deduplication /other	Comparison of codes to true incidence
		(disputed in correspondence) Piecewise/segmented regression analysis performed.	03819, 0411, 04110, 04119 Streptococcal endocarditis: 0380, 0382, 0410, 04100, 04101, 04102, 04103, 04104, 04105, 04109 Gram negative endocarditis: 04185, 0384, 03840, 03841, 03842, 03843, 03844, 03849, 0413, 0414, 0415, 0416, 0417 Fungal endocarditis: 1160, 1154, 11281		
Bor[226] 2013	**Timescale:** 1998-2009 **Country:** US **Population**:hospitalised patients **Study design**:time trends analysis using linear regression **Data source:** Agency for healthcare research and quality NIS database **Details:** .	Organisms coded for 62.3% of infective endocarditis discharges in 1998, 69.4% in 2009. Note likelihood of undercoding. Polymicrobial endocarditis in 4.2% Most common organism *S. aureus*, increase in proportion from 24.0-32% of infective endocarditis cases. No clear increase trend in Streptococcal endocarditis.	Admission with endocarditis code in any position : 4210 4211 4219 03642 09884 11281 1154. "Did not include 0.2% of cases where endocarditis was not in the first 15 diagnoses" Organisms listed in appendix	Number of hospital stays. Deduplication for transfers: Numbers of transferred patients calculated and subtracted from numbers. Acknowledge they will include readmissions.	No

Author and Year	Details	Finding	Case definition and codes used	Deduplication /other	Comparison of codes to true incidence
Mackie[227] 2016	**Timescale:** 2002-2013 **Country:** Canada **Population**:hospitalised patients **Study design**:interrupted time series analysis **Data source:** Canadian Institute for Health Information **Details:** , 8055 hospitalisations with a code of infective endocarditis.	Piecewise linear regression model with 2 trends before and after guidelines and a change point analysis. No change in slope at 2007. Increase in trend seen 2011 with decrease in trend of Streptococcal endocarditis. Suggest aging population and more devices (more pacemakers and defibrillators) Noted 73.8% had coexisting diagnosis. Rates 0.05 hospitalisations per month per 10 million	Admission with primary endocarditis code: ICD-9 421.0-421.9 or ICD-10 I33.0-I33.9) Additional data collected on organism coes rganism codes: ICD-9CM 041.x, ICD-10 B95.x) and sepsis codes (eg, ICD-9CM 038.x, ICD-10 A41.x)	All hospitalisations. Hospitalisations within 24hrs of patient being discharged from another acute care hospital-transfer and analysed as single hospitalisation	No, but discussion references Fedeli[235] and Schneeweiss[243] and good quality of Canadian data
Toyoda[228]: assessment of incidence 2017	**Timescale:** 1998-2013 **Country:** US **Population** California and new York state hospitalised patients **Study design**:retrospective population epidemiology study including segmented regression analysis **Data source:** US state databases	Standardized annual incidence stable: 7.8 /100,000. Native valve disease decreased, prosthetic valve disease increased, device related disease increased. Healthcare associated nosocomial decreased proportionally. No increase in oral Streptococcal endocarditis. Crude mortality stable, adjusted	Admission with Primary or secondary endocarditis code: 4210 4211 4219 11281 03642 09889 11504 11514 11594 Also data collected on organism codes: Oral streptococcus: 04100 04109 Streptococcus: 0380 0382 0410 04100 04101 04102 04103 04104	First admission only used. Repeat admissions and readmissions excluded.	Extensive validation in additional Note other studies with different findings may be affected by recurrences, relapses and transferred cases, and less specific ICD9 codes.

Author and Year	Details	Finding	Case definition and codes used	Deduplication /other	Comparison of codes to true incidence
	Details: 75,829 patients with first episode of endocarditis in	mortality increased.	04105 04109 0412 *S. aureus*: 03811 03812 04111 04112 Staphylococcus: 0381 03810 03811 03812 03819 0411 04111 04112 04110 04119 MRSA: 03812 04112 (after 2008) 03811 04111+v090 or V091 (pre 2008)		
Sakai-Bizmark[229] 2017 update	**Timescale:** 2001-2012 **Country:** US **Population**: Hospitalised patients<18 years **Study design**:Interrupted time series analysis **Data source:** Heathcare Cost and Utilization Project, NIS Agency for Healthcare Research and Quality **Details:** a . 3748 discharges 82% primary code 15% secondary code 3% tertiary code	Incidence 4.2 per 100,000. Post guideline change increased likelihood of streptococcal (23.8% vs 32.0%) and Viridans group streptococcal (VGS) cases (17.6% vs 24.2%). 70% cases had pathogen code, 65% preguideline, 75% post guideline. *S. aureus* most common (34%), streptococcus (27%). Overall increase in incidence, no change in trend pre and post guidelines. Increasing trend in VGS in	Hospitalisation with endocarditis code: 4210 4211 4219 Primary position, or secondary or tertiary position if primary/secondary code a relevant infective code following: (1) Pathogen codes; (2) Sepsis: 995.9; (3) Bacteremia: 790.7; (4) Septic Shock: 785.52; (5) Device Complication: 996–999; and (6) Pneumonia.	No deduplication due to use of NIS data, noted in discussion.	"Our initial review of data revealed that using only the principal diagnosis code for infective endocarditis may significantly decrease selection of true cases, at times finding pathogen as the principle diagnosis, and infective endocarditis as the secondary. " Also covered in discussion

Author and Year	Details	Finding	Case definition and codes used	Deduplication /other	Comparison of codes to true incidence
		older patients subgroup Indexed to hospital admissions, not population numbers			
Cresti[230] 2017 update	**Timescale:** 1998-2014 **Country:** Italy **Population**:patients referred to tertiary hospital for suspected infective endocarditis **Study design**:retrospective regression analysis of risk factors, cochra-amitage test for temporal trend **Data source:** prospective database **Details:** 1807 167 definite infective endocarditis (Duke criteria). Additionally, healthcare system database interrogated for discharge records with ICD9 codes – 194 patients, definite	Incidence 4.6/100,000 population, increasing linearly. *S. aureus* 25%, Coagulase negative Staphylococci (CNS) 22%. Staphylococcal disease associated with intravenous drug use (IVDU) and septic shock. Culture negative 11%.	Not specified clinician-diagnosed case). Codes used to identify possible case: 'endocarditis code' ICD-9	Covered in discussion.	Data provided: total 173 patients (ie database identified 6 extra, sensitivity 97%, coding identified 143/173 84%) 194 admissions, of which 25 (13%) had no criteria for definite infective endocarditis, 28 (14%) were readmissions. Discussed limitations of discharge-coding only studies

Author and Year	Details	Finding	Case definition and codes used	Deduplication /other	Comparison of codes to true incidence
	infective endocarditis in 143. Total 173 patients				
Gupta[231] 2017 update	**Timescale:** a 2000-2010 **Country:** US **Population**: hospitalised children **Study design**:trends assessed using linear regression **Data source:** NIS database 3840 hospitalisations of children <20 years.	Incidence 0.43/100,000. 30% of cases culture negative. Staphylococcal 43% Streptococcal 40%. Among culture-positive patients, increased proportion of Streptococcal cases ie, decrease in staphylococcal cases.	Admission with endocarditis code: Primary and secondary diagnoses, ICD-9 421.X 09884, 03642, 11281, 11504 11514 11594	None. Covered in discussion	Note limitations of ICD-9 coding use, no Duke criteria, and inclusion of readmissions/transfers.
Pasquali[232] 2012	**Timescale:** a **Country:** a **Population**:a **Study design**:a **Data source:** a **Details:** a 1157 infective endocarditis cases in children <18 years 2003-2010 at 37 centres in Paediatric Health Information Systems Database USA	Raw number of cases did not change over time. Indexing to number of hospital admissions showed decline in admissions. No population comparison.	4210 in any position plus 7 days of antibiotics within 7 days of admission. Oral streptococcal species (ICD-9 codes 038.0, 038.3, 041.00, 041.03, 041.05, 041.09) Those with codes for Group A, B, or D streptococcus, pneumococcus, or staphylococcus species were excluded.	First (index) hospitalization included	No

Author and Year	Details	Finding	Case definition and codes used	Deduplication /other	Comparison of codes to true incidence
Thornhill[244] 2018	**Timescale:** a **Country:** a **Population**:a **Study design**:a **Data source:** a **Details:** a Marketscan US healthcare insurance database (Medicare and Medicaid) 240 million individuals Jan 2000-Aug 2015	20,340 episodes of infective endocarditis. Poisson regression modelling before, during and after guideline change suggested decreasing rate prior to guideline change, with subsequent continuing downward trend with reduced rate of decrease. infective endocarditis cases/month/100,000 expected from pre-guideline trends 11.04, actual observed 30.57 cases/month/100,000	ICD-9 code 421.0, 421.1, or 421.9, primary or secondary discharge diagnoses	Continuous episodes counted once as per Thornhill 2011[245]. New episodes defined by first episode or readmissions if >6 months apart.	Not done
Assessments of coding accuracy					
Toyoda[228] additional: coding accuracy 2017	**Timescale:** a **Country:** a **Population**:a **Study design**:a **Data source:** a **Details:** a Mount Sinai data warehouse discharge data, text search 'endocarditis' or 'vegetation', or ICD9	Mount Sinai: Sens/Spec/PPV Primary: 21.1/99.9/96.6 Primary and Secondary (main analysis): 93.6/99.9/93.9 Prim minus 4249x: 95.5/99.9/80.1 Prim minus 4249x 2003-2005 PPV 89 (131 pts) Also reviewed types of	Primary or secondary 4210 4211 4219 11281 03642 09889 11504 11514 11594 Included, but low specificity noted 42490 42491 42499		

Author and Year	Details	Finding	Case definition and codes used	Deduplication /other	Comparison of codes to true incidence
	codes listed 2013-2014. 1673 hospitalisations, 515 hospitalisations, 283 patients with infective endocarditis. Further code validation at 5 other facilities	disease and organisms in 155 pts 2013/14. 5 separate hospitals, PPV 90, 93, 90, 90, 95, 97. (total 166 pts)			
Fedeli[235] 2011	**Timescale:** a **Country:** a **Population**:a **Study design**:a **Data source:** a **Details:** a 1863 subjects hospitalized for infective endocarditis in Italy Veneto region Linked mortality, linked microbiological database. 502 had organism code, 106 had blood culture data.	Increasing trend in infective endocarditis 2000-2008. Rate 4.4/100,000	421.x 98.84 (gonococcal endocarditis) 112.81 (156 Candida endocarditis) Used 38.c or 41.x microbiological codes but rarely reported.	Day cases excluded. Pre-2000 excluded. First hospitalization 2000-2008 counted.	Note lack of validation of ICD9 codes. Pilot investigation described in discussion: at a single Veneto hospital chart review of discharges and extraction of codes (including 421.x 98.84, 112,81, 93.2 391.1 and 424.9x 996.61 (T826 and T827) (note typo in the manuscript) against Duke criteria infective endocarditis. PPV 91/123, 81% PPV, sensitivity 91/98, 93%.
Schneeweiss[2 43] 2007	**Timescale:** a **Country:** a **Population**:a **Study design**:a	Overall specific PPV 80%/infection generally 90% Endocarditis: 14/19 were	421.x used Considered and excluded 036.42, 093.2x 098.84, 391.1, 397.9, 421.0	NA	NA

Author and Year	Details	Finding	Case definition and codes used	Deduplication /other	Comparison of codes to true incidence
	Data source: a **Details:** a Overall accuracy of bacterial infection coding, 127 patients with coded infections selected for review	true, with PPV 74%	421.9 422.92		
Sunder[246] 2015	**Timescale:** a **Country:** a **Population**:a **Study design**:a **Data source:** a **Details:** a French Regional Hospital Discharge Database (part of French Hospital Discharge Database) 2007-2009 2.53 million inhabitants. First: 243 stays 198 patients randomly selected and reviewed by ID specialist. 173 patients had infective endocarditis duke criteria. Second: 492 random patients post	First study: PPV 87.4% 128/173 definite, 44 possible, 1 insufficient data. Second study: NPV 99.4% PPV 100% sensitivity 90% specificity 100% These values used to adjust incidence estimates: infective endocarditis incidence 45.8 case per million Of microbiological code 309 patients (53.5%), 11% were non-specific bacterial infection, Streptococci 49%, staphylococci 36%.	Any position: I33 I38 I39 T826 Extensive codes listed in appendix Codes for infection due to pathogens responsible for infective endocarditis: A40 A48 A78 A395 A410 A411 A412 A413 A414 A415 A418 A419 A448 A449 A478 A479 A490 A491 A493 A498 A499 B376 B377 B960 B961 B962 B963 B964 B965 B966 B968	Ambulatory stays <24 hours excluded One episode per patient (justified as 2 year study, assumed same infective endocarditis episode)	

Author and Year	Details	Finding	Case definition and codes used	Deduplication /other	Comparison of codes to true incidence
	valve surgery, transoesophageal echocardiogram (TOE) or permanent pacemaker (PPM) removal				

Note: PPV=positive predictive value. NA=not applicable

Table 17: Summary of Endocarditis codes used in the above studies

Author	Other	I33.0 Primary	I33.0 Secondary	Other Primary	Other Secondary	I38 Primary	I38 Secondary	Organism codes
Tubiana[220] 2017		yes		I339				yes
Bates[221] 2017		yes	yes					
Bikdeli[222] 2013		yes	yes	4211 4219	4211 4219	4249	4249	
DeSimone[240] 2012		yes	yes					yes
Duval [241] 2012	Survey							
Van den Brink[242] 2017	Netherlands specific codes							
Dayer[223] 2015		yes						
Keller[224] 2017		yes	yes					yes
Pant[225] 2015		yes	yes	4211 4219	4211 4219			yes
Bor[226] 2013		4210	4210	4211 4219 03642 09884 11281 1154	4211 4219 03642 09884 11281 1154			yes
Mackie[227] 2016		I33 or		4219/I339				yes

Author	Other	I33.0 Primary	I33.0 Secondary	Other Primary	Other Secondary	I38 Primary	I38 Secondary	Organism codes
		4210						
Toyoda[228]: assessment of incidence 2017		yes	yes	yes	yes	yes		yes
Toyoda[228]: additional coding accuracy 2017		yes	yes	yes	yes	yes	yes	
Sakai-Bizmark[229] 2017		yes		Yes 4211 4219 If prim/sec code infective code				
Gupta et al[231] 2017 update		yes	yes	09884,03642, 11281, 11504 11514 11594	09884, 03642, 11281, 11504 11514 11594			yes
Pasquali[232] 2012		yes plus abx	yes Plus abx					yes
Fedeli[235] 2011		yes	yes	yes	yes			
Schneeweiss[243] 2007		yes						
Sunder[246] 2015		yes	yes	I39 T826	I39 T826	yes	yes	yes
Thornhill[244] 2018		yes	yes	4211 4219	4211 4219			

Note: abx=antibiotics. Numeric codes without letter prefixes are ICD-9 codes.

As described in **Table 16** above, some studies have found no significant change in disease trends after guidelines stopped recommending routine antibiotic prophylaxis for a broad range of at-risk individuals. Other studies suggest that any increase in overall incidence may be driven by an increasing population of "at-risk" older adults, including individuals with pre-disposing heart conditions and prosthetic devices[228]. The largest studies suggesting an increase in endocarditis incidence after guidelines changed used US health insurance data[244], and English Hospital Episodes Statistics (HES) data[223]. Given the lack of randomised controlled trials, these studies form some of the best available evidence; it is therefore important that the validity and accuracy of coding data, which these studies use, are comprehensively assessed.

The largest study investigating accuracy of endocarditis coding considered 1673 hospitalisations at a US centre, and found that sensitivity for identifying true infective endocarditis cases ranged from 21.1-97.2% depending on the definition of endocarditis, and diagnostic codes included[228]. In contrast, endocarditis coding quality in England has not been explored in detail to date; this is particularly relevant because it was an English study that suggested increasing incidence after changes in dental prophylaxis[223].

Given the importance of electronic health record data in endocarditis and beyond, and the utility of endocarditis as a case study given differences in coding algorithms in previous studies (**Table 17**), I investigated the quality of endocarditis diagnostic coding data in two English tertiary care centres, combining retrospective audit, service evaluation, linked electronic health record and microbiology data.

I first identified admissions with an endocarditis diagnostic code, and separately cases of infective endocarditis diagnosed by a clinician based on objective criteria. I then assessed the overlap between the two, that is, investigated to what degree admissions with a diagnostic

code represented clinical cases, and also compared incidence trends in both admission and clinical cases. Additionally I explored the reasons for any discrepancies.

4.2 METHODS

4.2.1 Study Population

Coding was studied in Leeds Teaching Hospital NHS Trust (Leeds), comprising seven tertiary and secondary care centres, directly serving a population of 780,000 with 1785 beds, and in Oxford University Hospitals NHS Foundation Trust (Oxford), a teaching hospital with three associated tertiary care centres, serving a population of 655,000 with 1465 beds[247].

4.2.2 Identifying diagnostic codes for infective endocarditis and secondary organisms

I reviewed all diagnostic codes from the WHO ICD-10 Version 5 containing the word 'endocarditis', together with codes used in previous publications related to infective endocarditis and causative organisms in electronic health records (**Table 17**, including ICD-10 equivalents of ICD-9 codes)[220,222,226-229,231,240,248], and codes used for confirmed clinical endocarditis cases in a 2016 audit of Oxford data. These codes were reviewed by three clinicians (Nicola Fawcett, Bernadette Young and Leon Peto) and the Oxford clinical coding team (Chris Middlemass and Sheila Weston) and classified as 'included in study' (represents infective endocarditis of non-viral aetiology) or 'not included' (represents disease entity other than as defined by standardised criteria), or 'not present in English data' (Error! Reference source not found.). Supplementary codes representing specific organisms were similarly

reviewed, and classified as representing the most common causative pathogens, *Streptococcus* spp., *Staphylococcus* spp., or other (Error! Reference source not found.).

4.2.3 **Data sources**

4.2.3.1 ***Clinical cases of infective endocarditis in Leeds: Endocarditis Service Database (Leeds)***

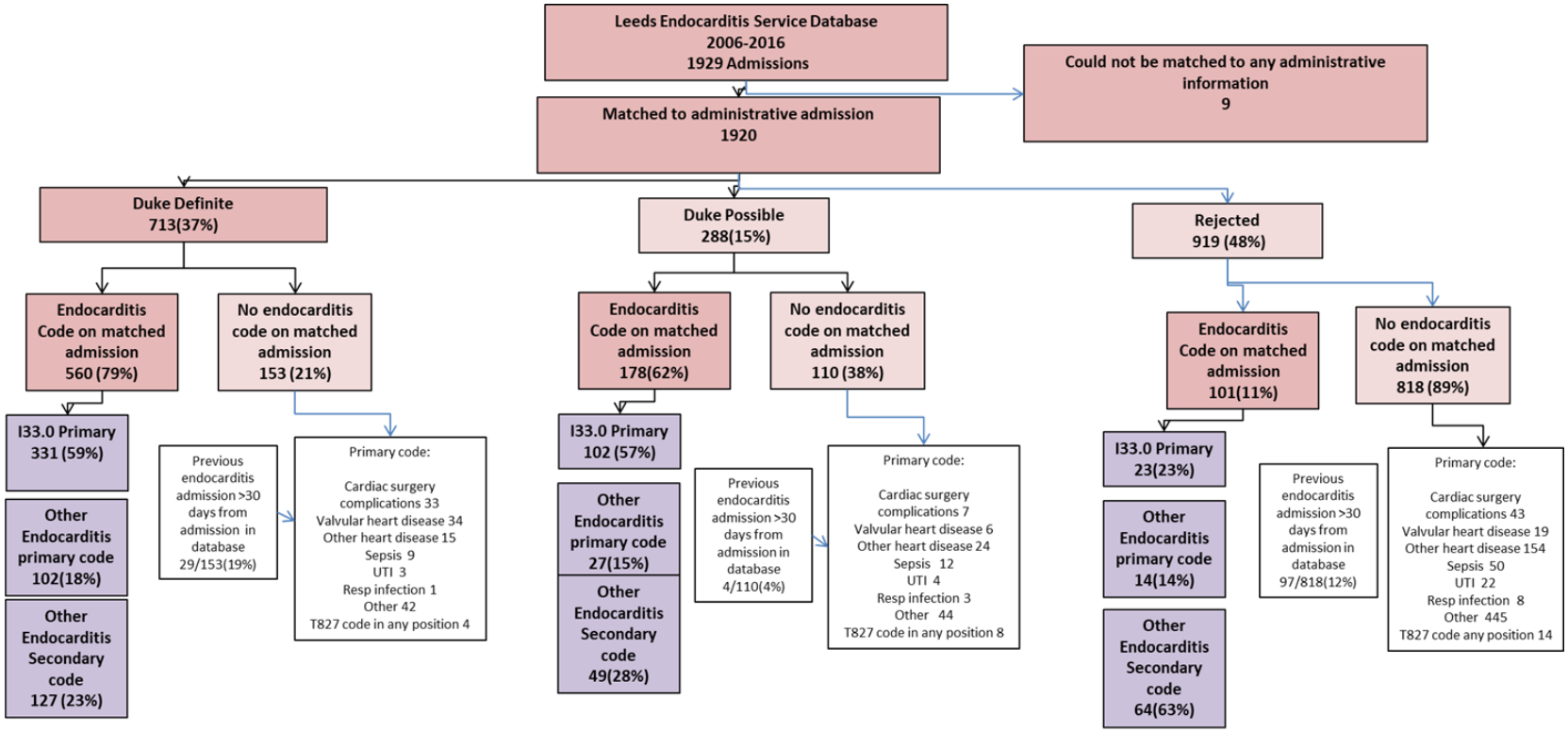
In Leeds, patients with suspected infective endocarditis referred by physicians across all sites have been reviewed by a dedicated team prospectively since 1st January 2006 and clinical details recorded in the Leeds Endocarditis Service Database, including modified Duke criteria[18,249] (definite, possible, rejected [i.e. investigated and excluded] – defined more completely in section 4.2.5 on page 170), causative organism genus, local patient identifier and admission dates (**Figure 11**). Electronic notes for admissions 2006-2016 with an endocarditis code but no corresponding record in the endocarditis service database were also reviewed retrospectively as part of a service evaluation exercise.

4.2.3.2 ***Clinical cases of infective endocarditis in Oxford: Clinical Audit***

In Oxford, electronic and paper notes from endocarditis-coded admissions 2010-2016 were retrospectively reviewed in an audit of endocarditis coding (**Figure 12**), conducted by three clinicians, Nicola Fawcett, Bernadette Young and Leon Peto. Ambiguous cases were reviewed by a second and if necessary third clinician, to achieve consensus by majority. A random set of 41 admissions were reviewed by two clinicians.

As this did not provide information on endocarditis cases which did not receive an endocarditis diagnostic code, I additionally reviewed notes from all patients who had antibiotics prescribed for infective endocarditis in Jan-Dec 2016, within a service evaluation

of antibiotic prescribing (**Figure 12**). Data prior to 2016 were not available as electronic prescribing was only implemented in late 2015.



Codes:
Cardiac surgery complications: T82.7
Sepsis: A41.x A40.x
Valvular heart issues: I34.x I35.x I36.x I37.x
Other heart issues: All I codes excluding valvular heart issues
UTI: N39.0
Respiratory infections: J0x , J2x

Figure 11: Clinical reviews in the Leeds Endocarditis Service database, Duke status and diagnostic codes

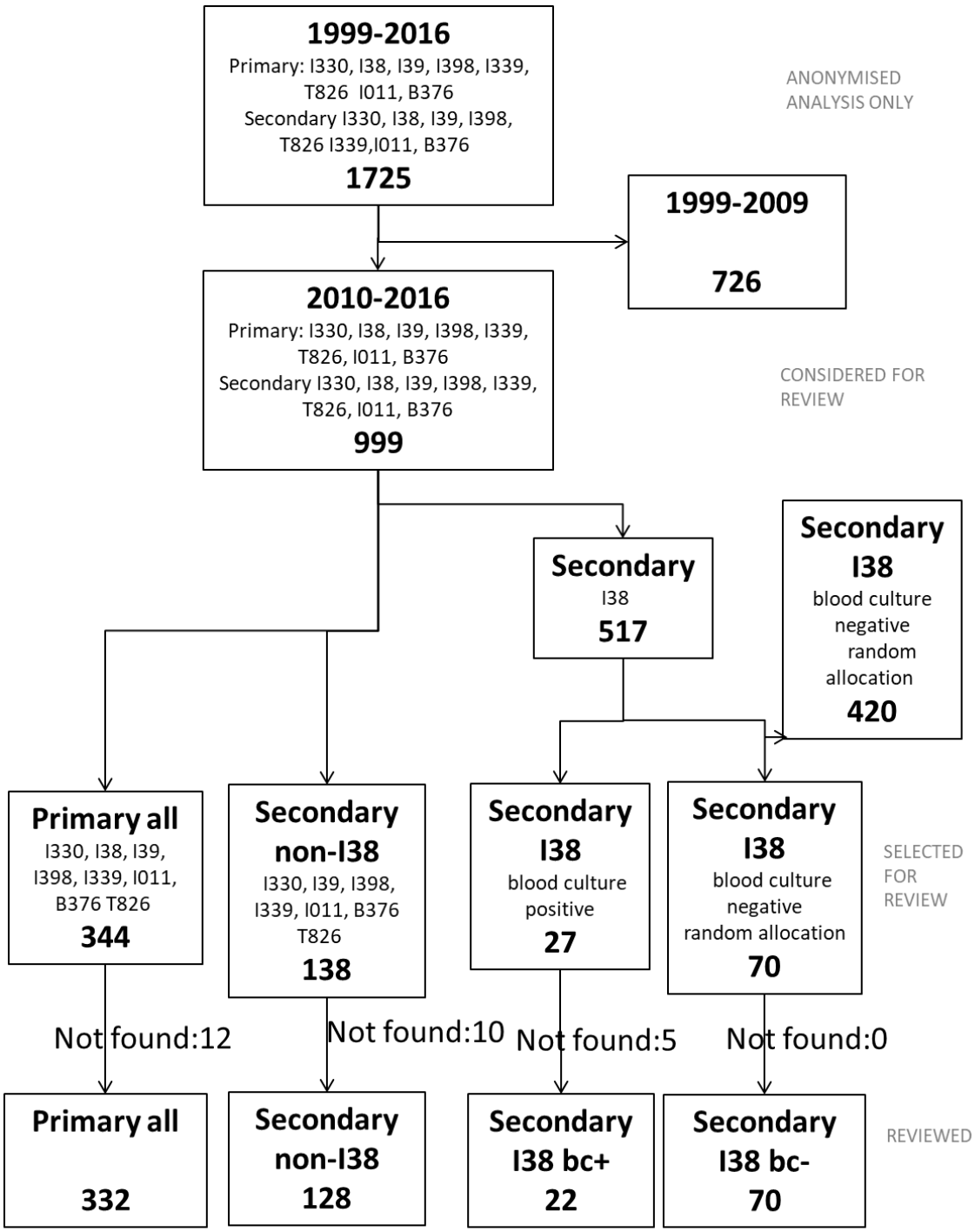


Figure 12: Admissions with an endocarditis diagnosis code and selection for review: Oxford

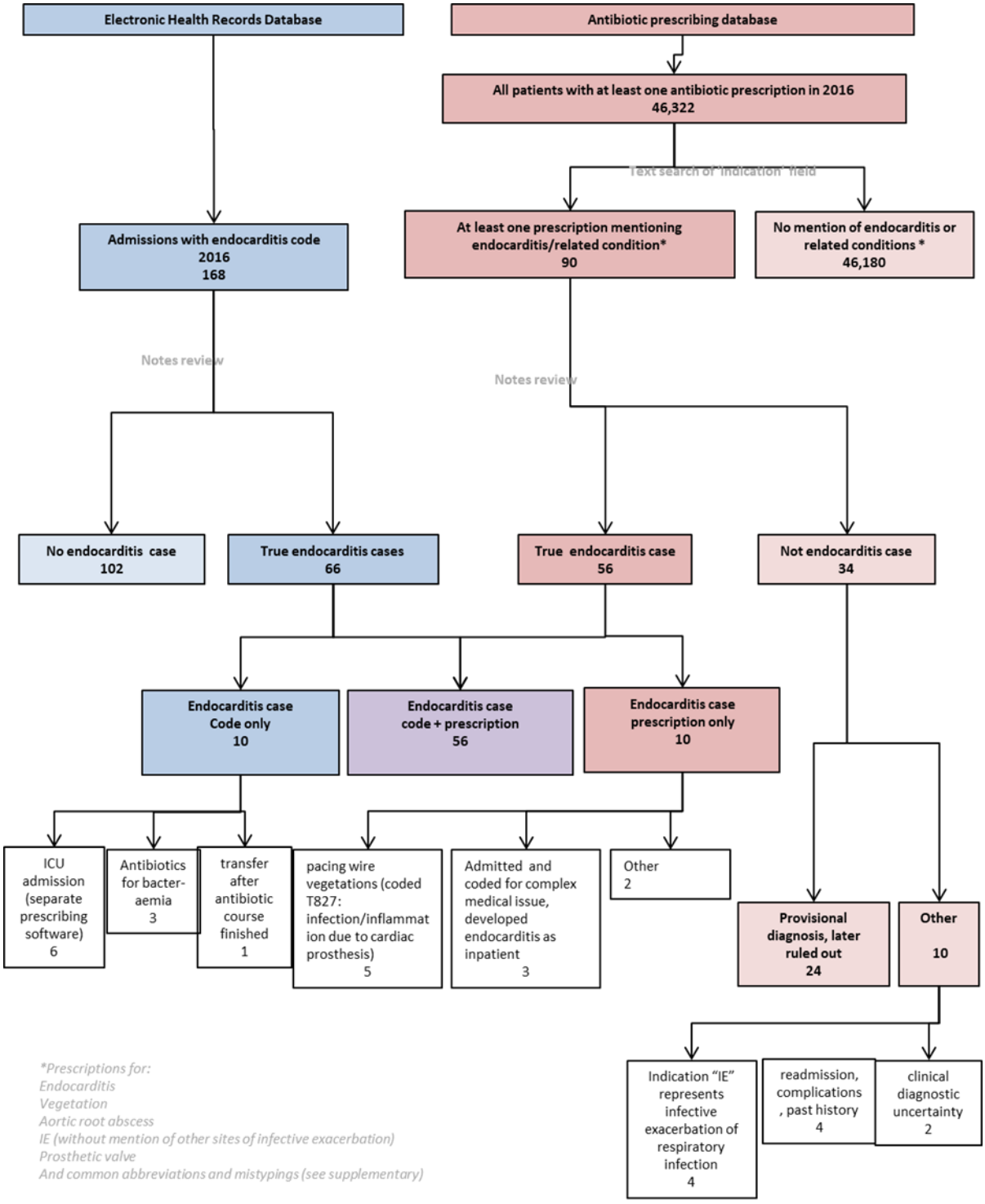


Figure 13: Review of electronic prescription data in Oxford 2016 with matching to coded data

4.2.3.3 *Electronic health record data*

In Leeds, electronic health record data were extracted from hospital databases as part of a service evaluation exercise for all admissions of patients in the Leeds Endocarditis Service Database, and all admissions with an endocarditis diagnostic code 2006-2016 inclusive. In Oxford, electronic health record data were extracted from hospital databases for all admissions during 2010-2016 with an endocarditis code, and for 2016 for admissions with a prescription indicating endocarditis. Data were extracted separately from an anonymised linked data warehouse[211] for all admissions with an endocarditis code from 1999-2016 for epidemiological analyses.

4.2.3.4 *Microbiological data on causative organisms*

For Leeds, organisms causing endocarditis were recorded by the clinician at diagnosis, based on microbiology results from a fully accredited UK microbiology laboratory, which followed standardised procedures in bacterial culture, identification and susceptibility testing[250-252]. For the Oxford 2010-2016 audit, causative organism was based on the organism recorded in the medical notes. For the Oxford 1999-2016 epidemiological analysis, causative organism was the organism isolated from blood culture (or *Bartonella/Coxsiella* serological testing) taken closest to the date of admission and during the admission, or up to 7 days preceding the admission if no organism was isolated during the admission. Organism identification was from a similarly-accredited UK microbiology laboratory. When calculating the percentages of causative organisms in Oxford, only direct admissions were analysed (all admission sources except 2A, 2B, 28 and 81, which represent patients transferred from another hospital e.g. "2B: transfer of an admitted patient from another hospital provider in an emergency"), so that patients with blood culture results from other hospitals/microbiology laboratories who were transferred to Oxford subsequently would not be included and falsely inflate the numbers of negative cultures or cultures not taken.

4.2.3.5 *Population data sources*

Population data was obtained from the Office of National Statistics, available for 2001-2016. Population data for the Leeds Local Authority District was used to represent catchment area for Leeds Teaching Hospital NHS trust, with 2016 data on population served (781,087) matching closely to quoted figures from official Trust reports of 780,000 in 2016[247]. The Trust takes a small number of referrals from other hospitals in the region, but this information was not recorded in the Leeds Endocarditis Service Database. Using Leeds population data only may thus slightly over-estimate incidence per population head, but given population growth was similar in Leeds and surrounding areas[253], should not affect incidence trends.

For Oxfordshire data, I included as a denominator the population in Oxford, South Oxfordshire, West Oxfordshire, Vale of White Horse and Cherwell Local Authority Districts (collectively part of Oxfordshire county), where Oxford University Hospitals is the tertiary referral service. The combined population data (678,484) closely matches trust reports for 2016/17 (655,000)[254].

For estimates incidence of endocarditis-coded admissions with blood culture data, results of blood cultures taken at time of admission were only available for patients admitted directly to the John Radcliffe Hospital (tertiary care centre in Oxford) or Horton Hospital (secondary care centre in Oxfordshire county). In this case, incidence per population head was calculated using the denominator of the population of the Oxford Local Authority District alone.

4.2.4 **Variables**

Anonymised electronic health record data extracted in Oxford and Leeds included admission/discharge dates, method of admission/discharge, and all diagnostic codes from all consultant episodes. In Oxford, data on blood cultures and *Bartonella/Coxsiella* serological testing as above were included from the anonymised linked data warehouse[211].

4.2.5 **Data processing**

Defining endocarditis cases

All cases (Leeds) and admissions (Oxford audit) evaluated as fulfilling modified Duke criteria[18,249] for possible or definite endocarditis were included in the analysis. Briefly, this guidance identifies major criteria and minor criteria (**Table 18**). Definite cases fulfilled 2 major criteria, 1 major criterion and 3 minor criteria or 5 minor criteria. Possible cases fulfilled 1 major criterion and 1 or 2 minor criteria, or 3 minor criteria.

4.2.6 **Classifying admissions with an endocarditis code in electronic health record data**

An admission was defined as a hospital provider spell ("the total continuous stay of a patient [..] on premises controlled by a Health Care Provider") according to NHS Business definitions[255]. Each spell comprised a number of consultant episodes, each with a primary ICD-10 code (the main condition treated or investigated) and up to 20 secondary codes for other relevant conditions and/or supplementary codes, e.g. reflecting organisms isolated (subsequently denoted 'secondary codes'). An admission with an endocarditis code was defined as any spell where an infective endocarditis code was used in any position of any consultant episode. If more than one endocarditis code was used during the spell, the primary code(s) was prioritised followed by secondary codes, with code priority being I33.0>I33.9>I39.0>139.8>I01.1>I09.1>I42.3>B37.6>T82.6>I38.0 based on *a priori* clinical plausibility and use in previous studies (Error! Reference source not found.). For admissions matched to an infective endocarditis case with no associated endocarditis code, I chose the dominant episode using previously reported methods to assess the coded reason for admission[189].

Table 18: Modified Duke Criteria for endocarditis, adapted from Li et al[28,29]

Major Criteria
Blood culture positive for infective endocarditis • Typical microorganisms consistent with infective endocarditis from 2 separate blood cultures: Viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*; or community-acquired enterococci, in the absence of a primary focus; or • Microorganisms consistent with infective endocarditis from persistently positive blood cultures, defined as follows: at least 2 positive cultures of blood samples drawn 112 h apart; or all of 3 or a majority of >4 separate cultures of blood (with first and last sample drawn at least 1 h apart) • Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer 11: 800
Evidence of endocardial involvement Echocardiogram positive for infective endocarditis (transesophageal echocardiogram (TEE) recommended in patients with prosthetic valves, rated at least "possible infective endocarditis" by clinical criteria, or complicated infective endocarditis [paravalvular abscess]; TTE as first test in other patients), defined as follows: • Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or • Abscess; or • New partial dehiscence of prosthetic valve • New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)
Minor Criteria
Predisposition, predisposing heart condition or injection drug use
Fever, temperature >38'C
Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions
Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor
Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with infective endocarditis. (Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.)

NOTE. TEE: transesophageal echocardiography

4.2.7 **Data matching**

All cases of infective endocarditis identified in the Leeds Service Database or Oxford 2016 prescribing evaluation were matched to admissions in electronic health record data except for 9 in Leeds, based on local patient identifier and nearest admission/discharge dates. In cases of multiple matches, I chose the admission with an endocarditis code (priority as above), followed by the longest admission during the clinician-recorded endocarditis dates. 9/1541 (0.006%) patients reviewed in Leeds could not be matched to any inpatient admission and were not considered further (**Figure 11**).

4.2.8 **Classifying cases, readmissions and prior history from matched clinical database and admissions data in Leeds 2006-2016**

To classify admissions as cases, readmissions or prior history, I first classified cases as those admissions that had direct overlaps of admission/discharge dates with clinician-recorded dates in the service database for any patient with Duke definite or possible endocarditis. Admissions that did not directly match a case of endocarditis were classified as readmissions for infective endocarditis if the admission occurred within 30 days of a discharge date of an admission matched to an endocarditis case. Any admission with an endocarditis case >30 days previously was counted as a past history. Length of stay was calculated as calendar date of discharge minus date of admission.

4.2.9 **Classifying cases, readmissions and prior history from the 2010-2016 clinician audit in Oxford**

Admissions were assessed as to whether the features a case of endocarditis were present according to modified Duke Criteria[18] by one of three clinicians as described in section

4.2.3.2. In the random set of 41 admissions reviewed by two clinicians, there were two discrepancies where one reviewer had mis-recorded a staphylococcal wound culture as being a blood culture, and another where one reviewer had not seen a third blood culture. As this duplicate review was done at the start of the process, and hence these issues highlighted for subsequent reviews,due to resource constraints, further multiple reviews were not done.

A clinical case was defined at audit as an admission where a new diagnosis of Duke definite/possible endocarditis was made (or a new genuine recurrence, including recurrence in a new prosthetic valve after surgery for infective endocarditis). A readmission was classified if the admission was for management of complications of a known prior episode of endocarditis, and the readmission date was within 30 days of a previous discharge date for endocarditis. A patient was defined as having a new, true second case of endocarditis (as opposed to failure of treatment/complication) if treatment for the prior episode had finished, and the managing clinician documented they felt it was a new case in the same patient. In the few cases where the patient was seen briefly as possible endocarditis and then sent home to await blood cultures, then readmitted later when cultures were flagged positive, the review counted the second admission as a clinical case, and the first, short admission as a readmission (technically a preadmission).

4.2.10 **Improving case identification using administrative data**

To improve identification of confirmed clinical cases from electronic health records, based on the findings of the comparisons of endocarditis-coded vs confirmed clinical cases from the Leeds service database and the Oxford audit, I examined the utility of excluding short stays, apparent readmissions and elective admissions. Based on clinical experience, it was judged unlikely that a patient with infective endocarditis would be admitted and discharged alive in less than 5 days. In the Oxford 2010-2016 audit, there were no admissions <3 days surviving to discharge that represented a case. In Leeds, 373 endocarditis-coded admissions <3 days

survived to discharge; only 3 (1%) were confirmed clinical cases. I therefore considered a threshold of <3 days (discharge date minus admission date) to exclude implausible endocarditis-coded admissions. It is possible that this strategy may result in excluding a small number of patients with infective endocarditis, anecdotally such as intravenous drug users who abscond. However given the low percentage of confirmed clinical cases excluded by this strategy, it was felt that overall it would improve case identification.

A normal treatment plan for endocarditis would be at least 6 weeks' antibiotics. In the Oxford 2010-2016 audit, two admissions of <6 weeks were confirmed clinical cases – both patients needed emergency valve surgery for the initial case of endocarditis, then developed endocarditis of the new valve with different organisms within 6 weeks, but after 30 days. As my aim was to investigate thresholds that minimised loss of true cases (and prioritised preserving sensitivity), I considered a threshold of <30 days from the previous discharge date to exclude readmissions.

Elective admissions are defined in administrative coding data as admission method 11 (waiting list), 12 (booked) or 13 (planned)[255]. The previous study of Dayer et al excluded waiting list admissions only. In Oxford, 33 elective admissions with an endocarditis code were identified; all were true elective admissions and 10 represented confirmed clinical cases, being elective admissions for valvular surgery and postoperative endocarditis (5, 3 and 2 were admission methods 11, 12 and 13 respectively). Similarly, in the Leeds service database, a number of Duke Criteria definite or possible cases had elective status. On review, these were similarly predominantly patients admitted for elective procedures who then developed endocarditis as an inpatient. However, as the most important previous English study had excluded some, but not all (for unclear reasons), elective admissions, I also considered excluding all elective admissions.

To combine these criteria, first, given its low positive predictive value (see Results), I excluded I38 where this occurred as a secondary code only. Second, I excluded any patients with a length of stay of 2 days or fewer (discharge date minus admission date, i.e. <3 days), that were discharged alive. Third, I removed coded admissions where the patient had a previous admission with an endocarditis code with admission date within 30 days of the previous discharge date. Performing the removal of admissions in this order meant that patients who were admitted twice, with one short and one long stay, would still be included if the short stay preceded the long stay. Fourth, I also considered removing elective admissions (admission method starting with "1"), but primary analyses did not exclude these "elective" patients for the reasons given above.

4.2.11 **Identifying confirmed clinical cases from prescribing data in Oxford**

For all electronic antibiotic prescriptions, Oxford implemented a mandatory 'indication' field to record reason for administration in accordance with UK Department of Health Guidance[9]. I searched for endocarditis cases using this mandatory 'indication' field which all clinicians have to complete to prescribe an antibiotic on the electronic prescribing system.

I searched all prescribing records January-December 2016 for the term "endocarditis" and compared it to confirmed clinical cases identified by the audit of admissions with an endocarditis code. I then converted all strings into lowercase and identified common misspellings like "rndocarditis" or "endocaritidis" that my initial text search would have missed. My best match was using a search of the string "ndoca" which incidentally resulted in no 'false' identifications.

I subsequently reviewed all patient records with an indication containing the text string "ndoca" "ie", "prosthetic valve", "aortic root" and "vegetation". "ie" identified a number of

infective exacerbations e.g. ie asthma, iecopd, so I subsequently restricted the text string to "ie" without "copd" "ild" "asthma" or "cf".

I noted there were 9 'true' infectious endocarditis cases that were missed through my text search, but it was not possible to design a text search for these, as they had indications "mssa bacteraemia"," liver abscess", "lung abscess", "cerebral abscess", and "infective endo. 18/8 dose"

4.2.12 Statistical methods

Analyses were performed using STATA 13.1. Incidence trends were estimated from annual counts using Poisson regression as there was no evidence of overdispersion ($p>0.4$), using population data for Oxfordshire and the Leeds area from the Office of National Statistics[253] for each year from 2001-2016 as an offset (imputing 2001 data for 1999 and 2000 in Oxford).

4.3 RESULTS

4.3.1 Less than half of admissions with an endocarditis code recorded in electronic health records represented a confirmed clinical case of infective endocarditis

1681 and 1725 admissions with an endocarditis diagnostic code in the primary or secondary position were identified in Leeds (2006-2016) and Oxford (1999-2016), respectively (**Figure 14**; flow diagrams in **Figure 11** and **Figure 12**, respectively). In Leeds 738/1681 (44%) endocarditis-coded admissions between 2006-2016 represented Duke definite/possible cases (**Figure 14** and **Figure 15**). In Oxford, 307/552 (56%) reviewed admissions between 2010-2016 represented Duke definite/possible cases (**Figure 14** and **Figure 15**).

4.3.2 Some codes used in most endocarditis studies had good predictive ability, but the frequently-used I38 code represented a confirmed clinical case in <6% of admissions

Not all diagnostic codes were equal – the code I33.0 ("Acute and subacute infective endocarditis") in the primary position ("the main condition treated or investigated during the relevant episode of healthcare"[196]), included in most endocarditis studies (**Table 17**), represented a new case in 433/530 (PPV 82%) and 231/273 (PPV 85%) reviewed admissions in Leeds and Oxford, respectively (**Figure 15**). Non-I33.0 codes and those in secondary positions performed less well, but some rarer codes nevertheless represented true cases, particularly in the primary position.

Among endocarditis secondary codes ("all conditions that co-exist at the time of admission, that develop subsequently, or that affect the treatment received and/or the length of stay"[196]), the code I38 ("Endocarditis, valve unspecified") was the most commonly used, but represented a new case in only 41/685 (PPV 6%) and 2/97 (PPV 2%) reviewed admissions in Leeds and Oxford, respectively (**Figure 15**). Of these 685 and 97 admissions with an I38 secondary code, 619 (90%) and 80 (82%) respectively had no mention of endocarditis in their medical notes, though many had some form of valvular heart disease. Both centres showed an apparent increase in the number of endocarditis-coded admissions over time, with sudden spikes at different time points (2015 in Leeds, 2012 in Oxford), driven largely by admissions with a secondary I38 code (**Figure 14**).

4.3.3 Discrepancies between codes and confirmed clinical cases were mainly due to correctly-assigned codes for readmissions, past histories and investigations for endocarditis (later excluded)

The majority of admissions with an endocarditis code that were not confirmed clinical cases had legitimate reasons for the code being assigned. A readmission or relevant past history accounted for 190/1681 (11%) and 53/552 (10%) endocarditis-coded reviewed admissions in Leeds and Oxford, respectively (**Figure 15**). Admissions where infective endocarditis was investigated and ruled out accounted for 101/1681 (6%) and 48/552 (9%) admissions in Leeds and Oxford, respectively. Discussions with the Oxford clinical coding team confirmed the NHS Clinical Classifications Service guidance[195] that a patient referred by a General Practitioner for 'suspected endocarditis', who had the diagnosis later excluded with no other definitive diagnosis confirmed would be correctly assigned a primary I33.0 code.

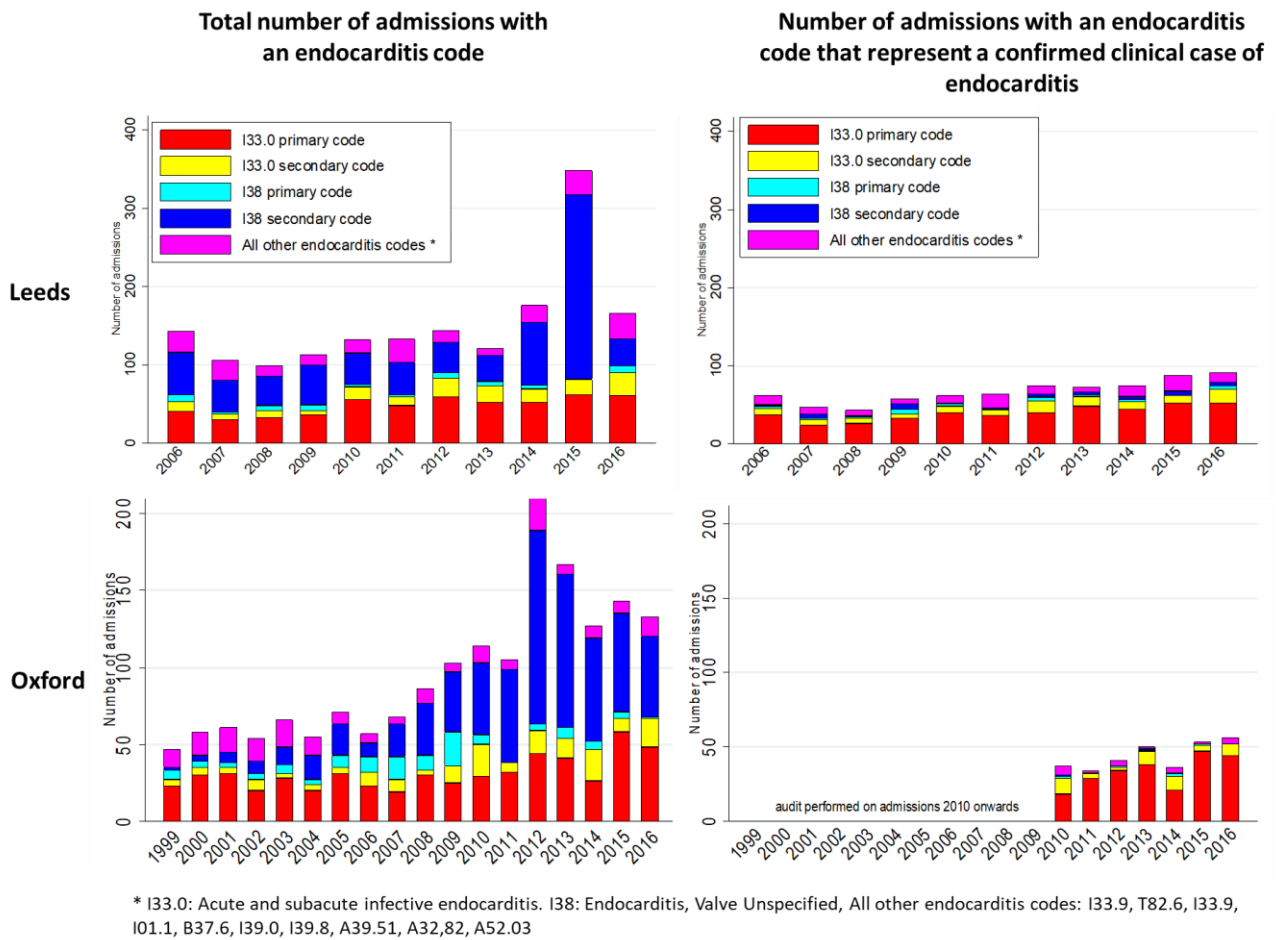


Figure 14: Numbers of admissions with endocarditis codes in Leeds and Oxford, compared to number those of admissions that represent a new clinical case

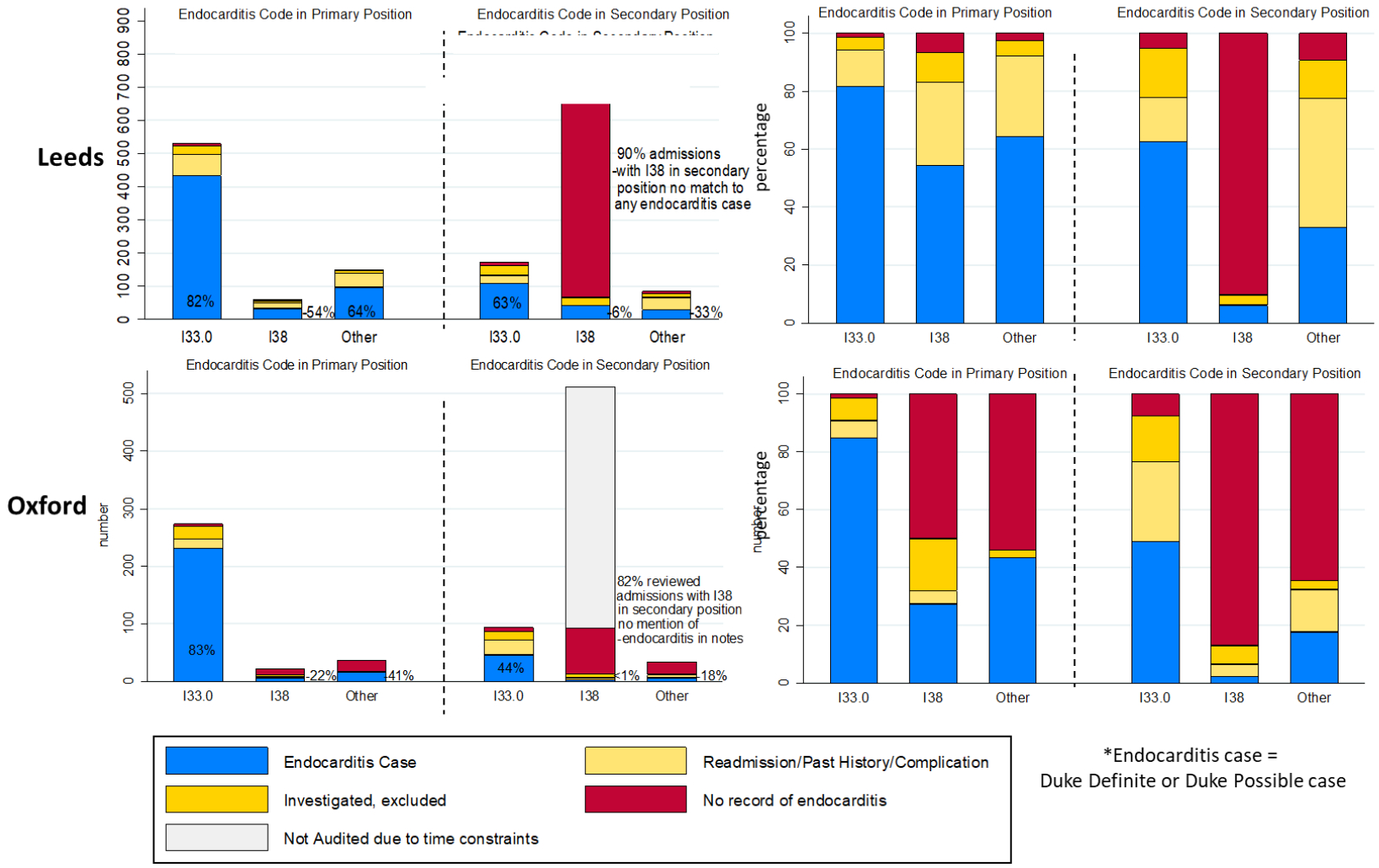


Figure 15: Clinical status of patients with endocarditis-coded admissions in Leeds and Oxford

4.3.4 I38: "Endocarditis: valve unspecified" could be correctly assigned even if endocarditis was never mentioned in the notes due to indexing guidance

Five admissions with a primary endocarditis code of I38 and no history of endocarditis were reviewed with the clinical coding team (Chris Middlemass and Sheila Weston) in detail, with the full coding process followed including use of both international and England-based[195,196] coding guidance and alphabetical indices[256], confirming the use of the I38 in the absence of clinical documentation of endocarditis.

Review of the coding process identified that the WHO-ICD-10 alphabetical index directs many nonspecific conditions towards an endocarditis code. For instance: "Stenosis-> valve (cardiac) (heart) (see also Endocarditis) I38". This was discussed with the Clinical Classifications Service, UK, the definitive source of clinical coding guidance who set the national standards for ICD-10 used by the NHS, who responded:

"The ICD-10 4th Edition is a classification, by the very nature of a classification the ICD-10 4th Edition code I38.X Endocarditis, valve unspecified, can be assigned when there is no mention of endocarditis in the medical record, but the ICD-10 alphabetical index directs you to assign a code from this category. Therefore, a coder would be correct to assign code I38 when indexing a documented diagnosis which leads the coder to assign code I38, even when the term endocarditis is not documented within the medical record."

-Clinical Classifications Service, Health and Social Care Information Centre, UK

4.3.5 Secondary codes often represent Duke definite/possible cases; primary codes miss a quarter of these cases

Patients who presented with embolic phenomena (e.g. stroke or cerebral abscess) due to infective endocarditis, or who developed infective endocarditis during an admission for valve surgery or chemotherapy, were commonly assigned a secondary endocarditis code, and a primary code reflecting the presentation, following coding guidelines. In Leeds and Oxford, 176/738 (24%) and 54/307 (25%) definite/possible cases with an endocarditis diagnostic code had this as a secondary code, respectively (**Figure 11** and **Figure 12**).

4.3.6 A quarter of Duke definite/possible endocarditis cases may not receive any endocarditis diagnostic code and are not readily identifiable using electronic health records

In Leeds, there were 1001 Duke definite/possible cases during 2006-2016 (

Table 19), of which 263 (24%) did not have an endocarditis diagnostic code associated with their admission (sensitivity 76%). This occurred less commonly for Duke definite (153/713 (21%)) versus Duke possible (110/288 (38%)) cases ($p<0.0001$). 52 (20%) missed cases had the code "T82.7: Infection and inflammatory reaction due to other cardiac and vascular devices, implants and grafts" present (in the primary or secondary position), but other primary codes covered a diverse range of infection, sepsis, and heart disease codes with no clear pattern (**Figure 11**).

Table 19: Reviews and Duke status in the Leeds Service Database and matching to endocarditis coded admissions

Duke Status	Both datasets	Coding dataset only	Clinical dataset only	Total
Definite	560	0	153	713
Possible	178	0	110	288
Rejected	101	0	818	919
---	0	842	0	842
Total	839	842	1,081	2,762

In Oxford, the audit of 2016 electronic prescribing records identified 10 additional cases above the 66 identified by diagnostic codes (**Figure 13**) (sensitivity 87%). Five had pacemaker lead infections with a code indicating an infected device, two were cancer patients developing infective endocarditis as inpatients, one had coding reflecting a septic, ischaemic foot and intensive care management with endocarditis found during the admission, one aortic root abscess had 'arteritis' written on a discharge summary and was coded as such, and one had coding for a mitral valve disorder with streptococcal sepsis.

4.3.7 Raw endocarditis-coded admissions data can give inflated estimations of incidence which can be mitigated by curation using carefully selected codes and other administrative data

Estimating cases of infective endocarditis using all admissions and all endocarditis codes (as defined in Error! Reference source not found.) overestimated the apparent incidence in Leeds during 2006-2016 by over twofold compared to confirmed clinical cases in the Leeds service

database (sensitivity/specificity/positive predictive value [PPV] 0.74/0.47/0.44 respectively) (**Table 20**, **Figure 16**).

I was able to substantially improve agreement between diagnostic codes and confirmed clinical cases by removing codes with low predictive potential (particularly I38 in a secondary position), very short admissions (<3 days) without death, and then (after excluding short admissions) readmissions within 30 days of a previous (endocarditis-coded) discharge date (see section 4.2.10, page 173). This combination substantially improved specificity and PPV, with only a small loss in sensitivity for Duke definite/possible cases in Leeds (0.69/0.89/0.78 respectively) (**Table 20**).

In Oxford, cases of endocarditis which do not have an endocarditis code would not have been included in this dataset, thus I could not estimate a true measure of sensitivity and negative predictive value. The percentage of true cases found during the audit that were correctly identified by coding/administrative data was calculated instead of sensitivity. Results were broadly similar (PPV 0.77) in Oxford (**Table 21** and **Figure 16**) compared to Leeds data.

To choose the strategy with the best overall performance, the data on sensitivity/specificity and PPV presented in Figure 16 show the tradeoff that has to be made, with lower sensitivity with strategies that increase specificity/PPV. As such, two analyses were performed - one for the 'most specific' strategy - I33.0 primary code only with short stays and readmissions removed - and one for the 'more inclusive' strategy. For the inclusive strategy, I chose to use all codes except I38 secondary, as using all endocarditis codes resulted in a big decrease in specificity/PPV.

Table 20: Agreement between different combinations of endocarditis-coded admissions and confirmed clinical cases in Leeds

Codes used	Removal of admissions with: <3 day LOS	readmissions <30 days	elective status	True Positive	False Positive	True Negative	False Negative	Sensitivity	Specificity	PPV	NPV
I33.0 primary only				433	97	1664	568	0.43	0.95	0.82	0.75
I33.0 primary only	✓			431	67	1694	570	0.43	0.96	0.87	0.75
I33.0 primary only	✓	✓		426	65	1696	575	0.43	0.96	0.87	0.75
I33.0 primary only	✓	✓	✓	406	57	1704	595	0.41	0.97	0.88	0.74
All primary codes				562	178	1583	439	0.56	0.90	0.76	0.78
All primary codes	✓			559	114	1647	442	0.56	0.94	0.83	0.79
All primary codes	✓	✓		552	111	1650	449	0.55	0.94	0.83	0.79
All primary codes	✓	✓	✓	529	96	1665	472	0.53	0.95	0.85	0.78
I33.0 in any position				549	162	1599	452	0.55	0.91	0.77	0.78
I33.0 in any position	✓			547	125	1636	454	0.55	0.93	0.81	0.78
I33.0 in any position	✓	✓		540	117	1644	461	0.54	0.93	0.82	0.78
I33.0 in any position	✓	✓	✓	514	102	1659	487	0.51	0.94	0.83	0.77
All primary and I33.0 secondary				669	242	1519	332	0.67	0.86	0.73	0.82
All primary and I33.0 secondary	✓			666	172	1589	335	0.67	0.90	0.80	0.83
All primary and I33.0 secondary	✓	✓		658	163	1598	343	0.66	0.91	0.80	0.82
All primary and I33.0 secondary	✓	✓	✓	629	141	1620	372	0.63	0.92	0.82	0.81
All codes except I38 secondary				697	299	1462	304	0.70	0.83	0.70	0.83
All codes except I38 secondary	✓			694	209	1552	307	0.69	0.88	0.77	0.84
All codes except I38 secondary	✓	✓		686	196	1565	315	0.69	0.89	0.78	0.83
All codes except I38 secondary	✓	✓	✓	653	168	1593	348	0.65	0.91	0.80	0.82
All codes				738	943	818	263	0.74	0.47	0.44	0.76
All codes	✓			735	573	1188	266	0.73	0.68	0.56	0.82
All codes	✓	✓		726	538	1223	275	0.73	0.69	0.57	0.82
All codes	✓	✓	✓	693	487	1274	308	0.69	0.72	0.59	0.81

Note: total number of clinically confirmed endocarditis cases=true positives+false negatives (1001); total number of endocarditis admissions=sum of all four columns (2762). LOS=length of stay.

Table 21: Agreement between different combinations of endocarditis-coded admissions and confirmed clinical cases in Oxford

Codes used	Removal of admissions with: <3day LOS	readmissions <30 days	elective status	True Positive	False Positive	True Negative	False Negative	Proportion audit true cases correctly identified	Specificity	PPV	Proportion audit non-cases correctly identified
I33.0 primary only				231	42	203	76	0.75	0.83	0.85	0.73
I33.0 primary only	✓			230	33	212	77	0.75	0.87	0.88	0.73
I33.0 primary only	✓	✓		228	26	219	79	0.74	0.89	0.90	0.74
I33.0 primary only	✓	✓	✓	223	23	222	84	0.73	0.91	0.91	0.73
All primary codes				253	79	166	54	0.82	0.68	0.76	0.76
All primary codes	✓			252	53	192	55	0.82	0.78	0.83	0.78
All primary codes	✓	✓		249	45	200	58	0.81	0.82	0.85	0.78
All primary codes	✓	✓	✓	243	38	207	64	0.79	0.85	0.87	0.76
I33.0 in any position				281	90	155	26	0.92	0.63	0.76	0.86
I33.0 in any position	✓			277	65	180	30	0.90	0.74	0.81	0.86
I33.0 in any position	✓	✓		273	46	199	34	0.89	0.81	0.86	0.85
I33.0 in any position	✓	✓	✓	265	39	206	42	0.86	0.84	0.87	0.83
All primary and I33.0 secondary				299	127	118	8	0.97	0.48	0.70	0.94
All primary and I33.0 secondary	✓			295	85	160	12	0.96	0.65	0.78	0.93
All primary and I33.0 secondary	✓	✓		290	65	180	17	0.95	0.74	0.82	0.91
All primary and I33.0 secondary	✓	✓	✓	281	54	191	26	0.92	0.78	0.84	0.88
All codes except I38 secondary				305	155	90	2	0.99	0.37	0.66	0.98
All codes except I38 secondary	✓			301	110	135	6	0.98	0.55	0.73	0.96
All codes except I38 secondary	✓	✓		294	89	156	13	0.96	0.64	0.77	0.92
All codes except I38 secondary	✓	✓	✓	284	69	176	23	0.93	0.72	0.81	0.88
All codes				307	245	0	0	1.00	0.00	0.56	0.00
All codes	✓			303	158	87	4	0.99	0.36	0.66	0.96
All codes	✓	✓		296	138	107	11	0.96	0.44	0.68	0.91
All codes	✓	✓	✓	286	115	130	21	0.93	0.53	0.71	0.86

Note: Based on all admissions 2010-2016 with an endocarditis code reviewed during clinical audit (N=552). Cases of endocarditis which fulfil Duke definite/possible criteria counted as true cases (n=307; sum of true positive and false negative). LOS=length of stay, readm=readmission.

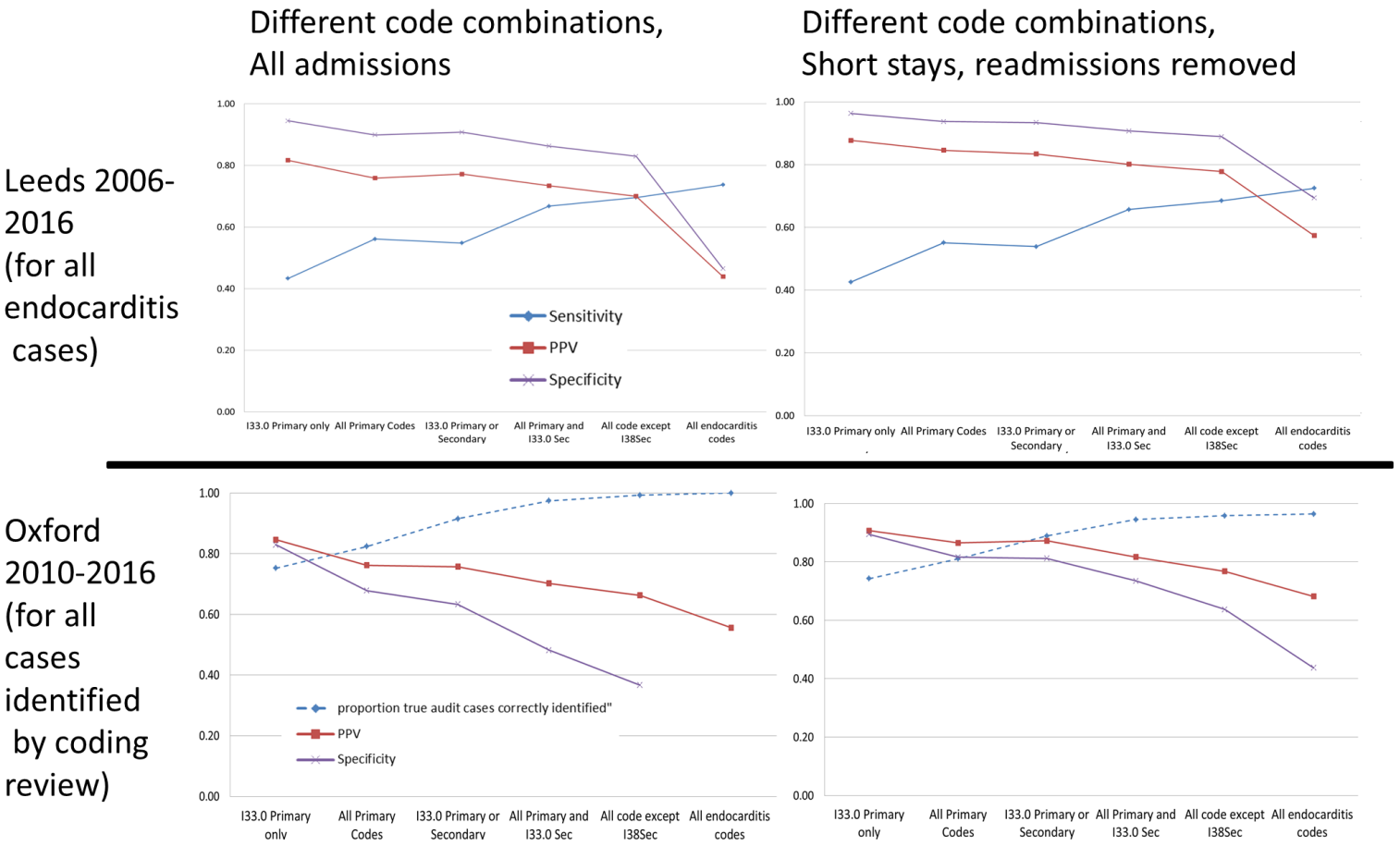


Figure 16: Sensitivity/specificity and positive predictive values for different algorithms to identify Duke definite/possible endocarditis cases from diagnostic codes in Leeds and Oxford

Note: Sensitivity is upper bound in Oxford providing all true cases have been identified by at least one code. Different definitions ordered by PPV

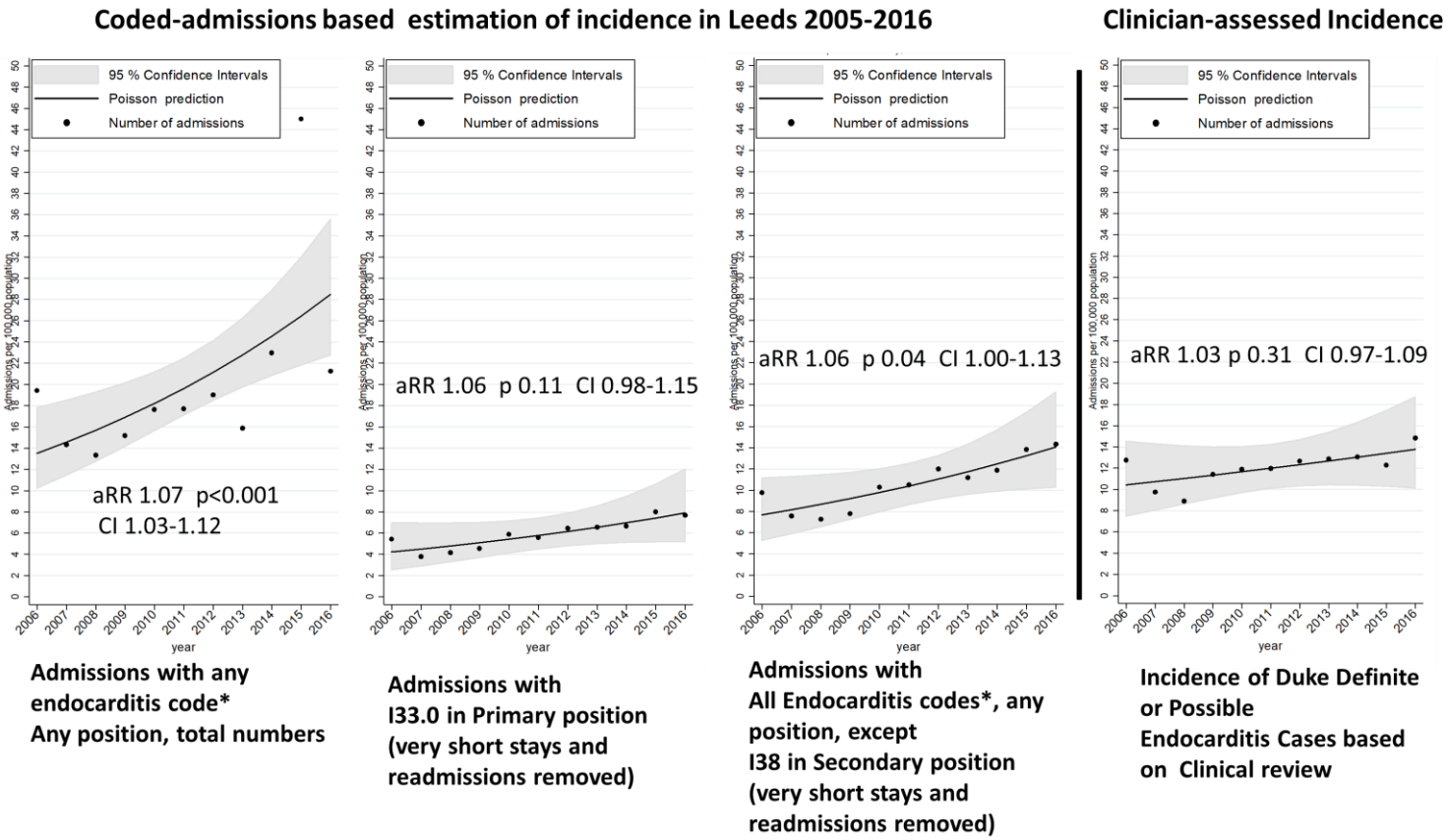


Figure 17: Annual incidence of endocarditis in Leeds as estimated by electronic health records, compared to confirmed clinical cases

*any endocarditis code = I33.0, I33.9,I39.0,139.8,I01.1,I09.1,I42.3,B37.6,T82.6,I38. aRR=adjusted relative risk ratio, CI= 95% Confidence Interval

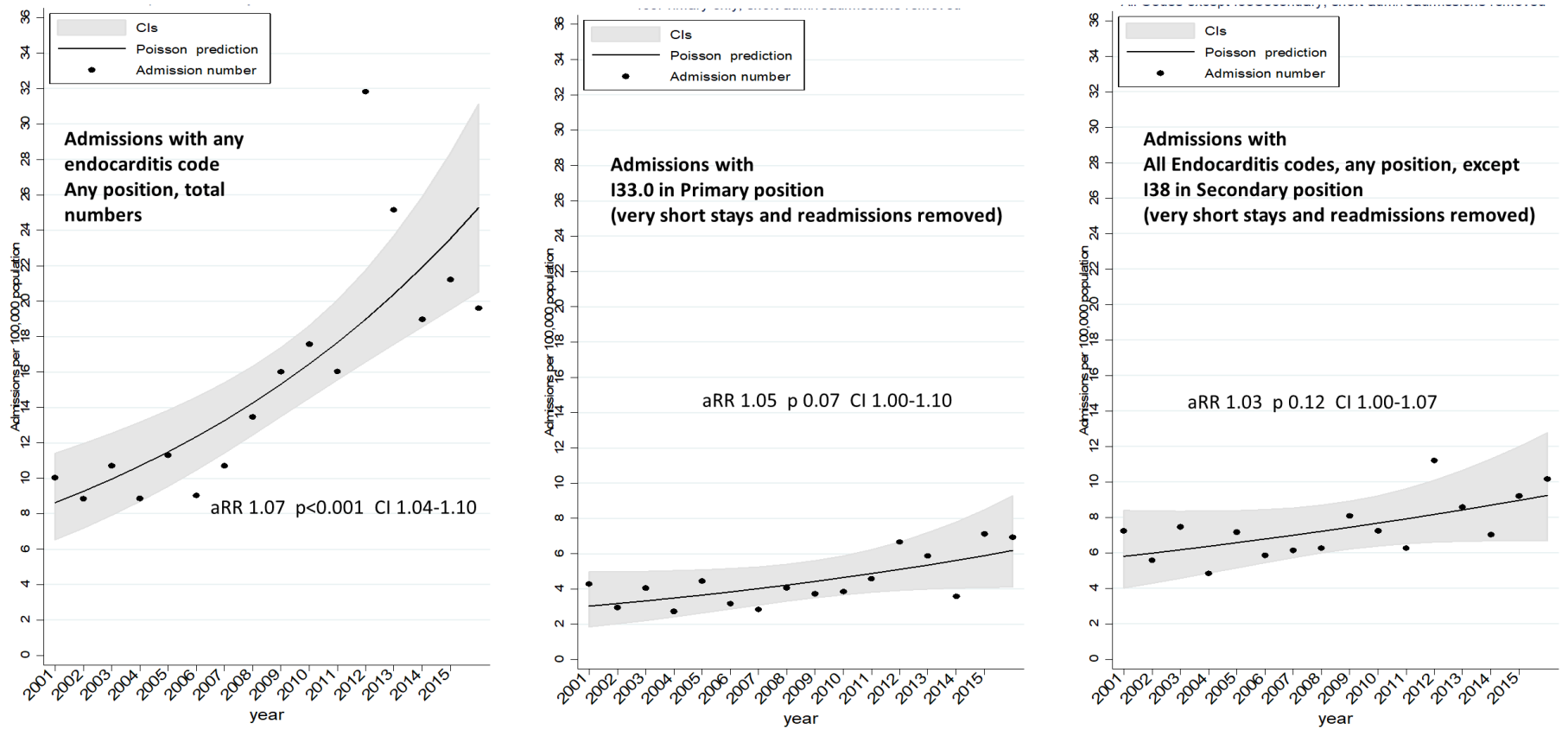


Figure 18: Estimated endocarditis incidence in Oxford based on diagnostic coding and administrative information

*any endocarditis code = I33.0, I33.9,I39.0,139.8,I01.1,I09.1,I42.3,B37.6,T82.6,I38. aRR=adjusted relative risk ratio. CI= 95% Confidence Intervals

4.3.8 Strategies that maximise positive predictive value can miss over half of cases

The majority of studies of endocarditis incidence use only the ICD-10 code I33.0, or only the I33.0 and I33.9 codes (or ICD-9 equivalents). Using I33.0 in any position had similar specificity and PPV in the Leeds data to the strategy above (removing I38 in a secondary position, very short admissions (<3 days) without death, and then readmissions within 30 days of a previous (endocarditis-coded) discharge date) but with reduced sensitivity (sensitivity/specificity/PPV 0.55/0.91/0.77) (**Table 20**). The strategy with the highest PPV (88%) used I33.0 in the primary position alone[223,245] but also removed short stays, readmissions and elective admissions. However, despite its high specificity (0.97), this strategy had reduced sensitivity (0.41) (**Table 20** and **Figure 16**), and hence underestimated overall incidence (**Figure 17**). Including short stays, readmissions and all elective admissions with the I33.0 primary code, more similarly to studies on English HES data[223,245], reduced the PPV to 82%.

4.3.9 Incidence trends depend on specific diagnostic coding algorithms

There was strong evidence of upward trends in incidence of uncorrected endocarditis-coded admissions per 100,000 population in Leeds (annual rate ratio, aRR=1.07 (95% CI 1.03-1.12) p<0.001), whilst confirmed clinical cases occurred at much lower incidence and showed smaller incidence increases (aRR=1.03 (95% CI 0.97-1.09) p=0.31) (**Figure 17**). Estimating incidence using the steps outlined above (removing codes with low predictive power, short stays and readmissions) substantially improved agreement between estimated and true incidence of endocarditis, although it still tended to overestimate incidence increases and suggest stronger statistical evidence to support them (**Figure 17**), whether based on all codes except I38 secondary or using only the highly specific I33.0 code in the primary position

(although the latter also tended to underestimate incidence). Similar estimated incidence patterns were seen in Oxford (**Figure 18**), but as information on confirmed clinical cases was only available from 2010-2016 in this dataset, no comparison in trends was possible.

4.3.10 Estimating incidence of streptococcal endocarditis using secondary codes can overestimate increases over time

Not unexpectedly, in endocarditis-coded admissions and confirmed clinical cases, the most common organisms associated with endocarditis were *Streptococcus* spp. and *Staphylococcus* spp. There are no diagnostic codes for the oral viridans-group *Streptococcus* species, which are most likely to be affected by changes in dental prophylaxis, so I was unable to compare trends in these organisms. Estimating the incidence of streptococcal endocarditis based on the presence of secondary *Streptococcus* codes in endocarditis-coded admissions suggested an increase over time in both Leeds and Oxford (p=0.04 and p=0.03 respectively, **Figure 19**). This apparent upward trend was not seen when the incidence of streptococcal endocarditis was calculated using confirmed clinical cases in Leeds (p=0.22) or using information from linked blood culture results in Oxford (p=0.41) (**Figure 19** and **Figure 20**).

4.3.11 Increased use of secondary codes over time may contribute to the apparent overestimation of streptococcal cases

In Leeds there was moderate agreement between streptococcal codes and *Streptococcus* spp. as cause of disease. Of 314 cases judged to be of single organism streptococcal aetiology by the clinician, 201 (64%) had an associated streptococcal code (kappa=0.56); 94 (30%) had no organism code and 19 (6%) had a different organism code (**Table 22**). Thus, where a code was given in both sources, the agreement was 91% (201/220). In Oxford, overall agreement

between linked blood culture results and coded organisms was similar: of 183 endocarditis-coded admissions with a linked positive streptococcal blood culture alone, 107 (58%) had a *Streptococcus* code, 68 (37%) had no code and 8 (4%) had another organism code (kappa=0.43) (**Table 23**); corresponding to 93% (107/115) agreement where a code was given. Use of secondary/supplementary organism codes, and secondary codes overall, increased substantially during the study period in both centres.

4.3.1 The commonest causative organisms seen in both Leeds and Oxford were *Streptococcus spp.* and *Staphylococcus spp.*

In Leeds, according to clinician collected data on causative organisms in Duke definite/possible cases, the commonest causative organism group were *Staphylococcus spp.* (372/1001 cases 37%) *Streptococcus spp*. (314/1001 cases 31%) (**Table 22 and Figure 20**). The exact species was not available, and thus I was unable to differentiate oral viridans-group Streptococci from other Streptococci, and were unable to differentiate cases caused by S.aureus and coagulase-negative *Staphylococcus spp.* in Leeds. *Enterococcus spp.* were the next most common cause (99/1001 10%), 122/1001 (12%) being considered due to other organisms and 27/1001 being considered polymicrobial (3%). 7% were considered true culture negative cases (67/1001).

In Oxford, based on blood culture data linked to direct admissions with an endocarditis code (using our algorithm – all endocarditis codes except I38 secondary position, with short stays and readmissions removed), similar results were seen in terms of most common organisms. Data was available at a species level (**Table 23 and Figure 20**). Using our algorithm to identify endocarditis admissions (all codes except I38 secondary, short stays and readmissions removed), *Staphylococcus spp.*were the most commonly seen organism in blood cultures linked to the admission, in 190/880 (22%) cases, of which 121/880 (14%) were *S. aureus*. In 183/880 (21%) admissions, the linked blood culture was a *Streptococcus spp.*

After this, again similar to Leeds, *Enterococcus spp.* were the next most common with 62/880 (7%) of admissions, 61/880 (7%) being due to other organisms, and 10/880 (1%) being considered Polymicrobial. However in Oxford, the percentage of apparent 'culture negative' cases was larger, with 242/880 (28%) having no positive cultures linked (but at least one culture with no growth) and 132/880 (15%) having had no cultures taken. The cause for this large number of culture negative cases was not immediately apparent. It is worth noting highest percentage of culture negative cases was in the final year of data (**Figure 20**).

Table 22: Coded organism vs clinician recorded organism in Leeds Duke definite/possible cases

	Clinician recorded cause (genus level only)						
Organism code	*Streptococcus*	*Staphylococcus*	*Enterococcus*	Other	Polymicrobial	None	Total
Streptococcus	201	2	44	13	6*	4	270
Staphylococcus	13	254	4	10	10**	6	297
Other	6	0	16	23	1+	1	47
None	94	116	35	76	10#	56	387
Total	314	372	99	122	27	67	1001

* 5 mixed Streptococcus and Staphylococcus, 1 Enterococcus/Staphylococcus.

** 5 mixed Staphylococcus and Streptococcus, 1 Streptococcus and Other, 3 Staphylococcus and Enterococcus and 1 Staphylococcus and Other.

+ 1 mixed Staphyloccocus and Other.

4 mixed Streptococcus and Staphylococcus, 4 mixed Staphylococcus and Other, 1 Enterococcus and Other, and 1 Other and Other.

Note: Of 614 cases where an organism code was given, 455 (74%) agreed exactly to the level of Streptococcus and Staphylococcus spp. (noting that Enterococcus may be coded as Streptococcus given the options available). Of 475 clinician-determined Streptococcal/Staphylococcal cases, 455 (96%) were correctly identified from organism codes.

Table 23: Coded organism vs microbiology blood culture organism in all admissions with a non-I38 endocarditis code in Oxford

	Microbiology linked blood culture results (species level)									
Codws organism	Non-oral *Streptococcus spp.*	Oral *Streptococcus spp.*	*Enterococcus spp.*	*Staphylococcus aureus*	*Coagulase-negative Staphylococcus spp.*	Other	Polymicrobial	Negative cultures	None taken	Total
Streptococcus	34	73	15	0	4	4	1*	47	22	200
Staphylococcus	1	7	1	98	33	6	5**	44	20	215
Other	0	0	11	1	1	4	0	5	4	26
None	23	45	35	22	31	47	4#	86	86	439
Total	58	125	62	121	69	61	10	242	132	880

* 1 mixed Enterococcus and Staphylococus.

* 3 mixed Staphylococcus and Enterococcus, 2 mixed Staphylococcus and Streptococcus.

mixed Streptococcus and Enterococcus, 3 mixed Staphylococcus, Streptococcus and Other.

Note: Of 441 cases where an organism code was given, 238 (41%) agreed exactly to the level of Streptococcus and Staphylococcus spp. (Enterococcus may be coded as Streptococcus given the options available). Of 252 microbiology-determined Streptococcal/Staphylococcal cases, 238 (94%) were correctly identified from organism codes.

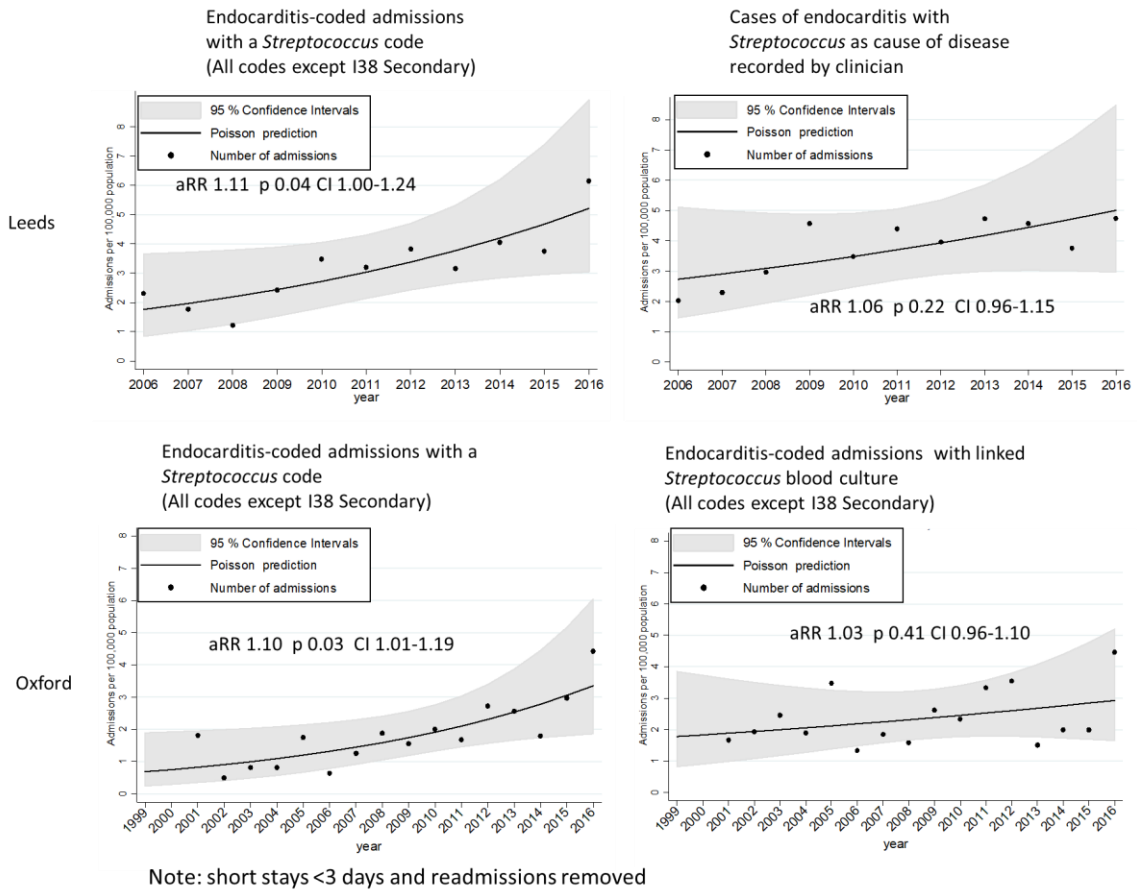


**Figure 19: Comparison of endocarditis-coded admissions with a Streptococcus code, and confirmed clinical cases or blood culture data in Oxford and Leeds ***any endocarditis code = I33.0, I33.9,I39.0,139.8,I01.1,I09.1,I42.3,B37.6,T82.6,I38, aRR=adjusted relative risk ratio, CI= 95% Confidence Interval

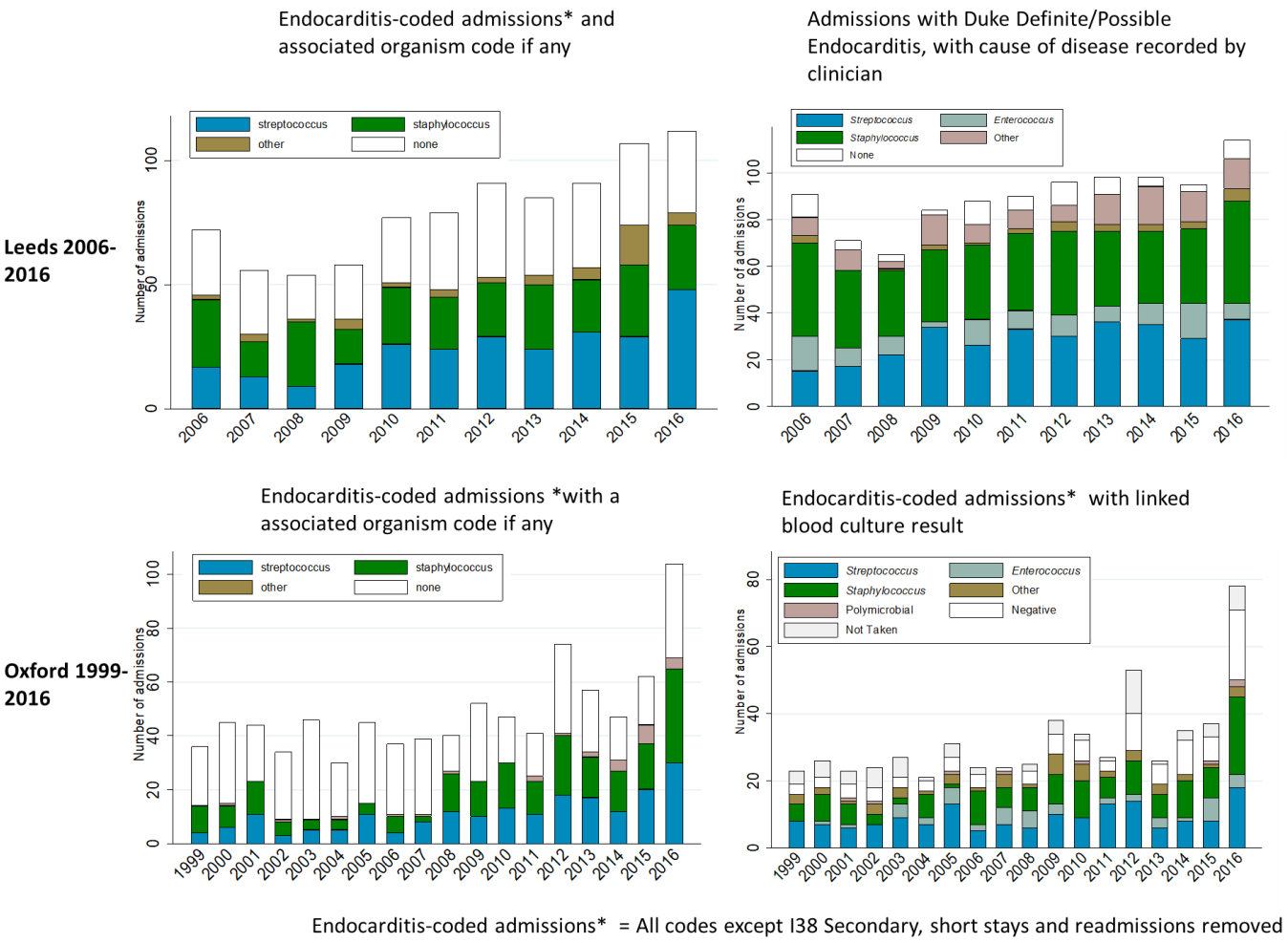


Figure 20: Comparison of coded organism and clinician recorded organism (Leeds) or blood culture organism (Oxford)

4.4 DISCUSSION

4.4.1 Main findings

Here, I aimed to use endocarditis as a clinically relevant case study to explore the relationship between clinical cases and diagnostic codes and quantify and understand discrepancies**.** By investigating the quality of coded infective endocarditis data in two large teaching hospitals, recorded between 1999 and 2016, I found that different diagnostic codes vary widely in their accuracy at identifying confirmed clinical cases. Poor specificity of coding data could be explained by several legitimate coding practices; for example, the coding protocol legitimately allows diagnostic codes with the word 'endocarditis' to be applied to readmissions and investigations for infective endocarditis, and even to admissions with no endocarditis issues at all. I have, however, shown that the overall accuracy of coding data can be improved by careful and critical selection of codes, removal of records with implausibly short stays and removal of readmissions. My study has also shown that using secondary/supplementary codes to estimate incidence of streptococcal endocarditis can give misleading incidence trends, likely due to increasing use of such codes over time. When used, the organism codes were reasonably accurate at species level in the two centres included in this study; this suggests they could be used to assess changes in proportions of differently coded organisms over time, provided there was careful consideration of potential for large-scale changes in coding behaviour, such as incentivisation to record specific organisms, in other studies.

4.4.2 **Study strengths**

This study, which used clinician-collected prospective data in Leeds and retrospective audit data in Oxford, based on objective clinical criteria, is the largest and most detailed study of endocarditis coding accuracy to date with 2,233 patient admissions reviewed, and is the first in a UK setting. It is the first to identify and quantify the reasons for discrepancies between admissions with a diagnostic code and clinical cases. Another major study strength was the availability of detailed microbiological data on causative organism, via clinician-recorded causes in Leeds, and linked microbiological data in Oxford.

4.4.3 **Study limitations**

Study limitations include the dual-centre nature of the study, and the limited information on confirmed clinical cases in Oxford. In Oxford, where secondary/supplementary codes were matched to blood culture data, mismatches might also be due to patients having positive blood cultures from infections other than endocarditis. The organism codes do not identify the oral viridans group streptococci, which are most relevant to changes in antibiotic policy, and I did not attempt to identify them from coding data, focussing on genus level comparisons. This study did not set out to investigate temporal associations between changes in antibiotic prophylaxis policy and endocarditis incidence, due to limited power with only two centres, but to assess the relationship between endocarditis-coded admissions and confirmed clinical cases. Previous studies investigating temporal associations using administrative coding data have varied in their findings[221,222,240 223,244]. These studies benefit from far larger numbers than my study; although generally they have not investigated the relationship between diagnostic codes and confirmed clinical case, except for Toyoda *et al*[228]. Most have used a restricted set of codes with reasonable performance in my study (**Table 17**). We also did not have any data on whether the number of individuals at high risk had changed

over time, such as individuals with prosthetic valves, or intravenous drug users. Dayer et al assessed valve surgery frequency based on procedure coding in HES data, and saw a sudden increase in coding for prosthetic material repairs in congenital heart disease from 2005 onwards. It was not clear whether this was due to a change in use of procedure codes or a change in practice. Otherwise there was a steady increase in all valve replacements 2000-2012, with a decrease in mechanical valve replacements and an increase in bioprosthetic valve replacements and valve repairs.

4.4.4 Comparisons to other studies

Two other US[228] and Canadian[257] studies of 1,673 and 119 hospitalisations, respectively, have assessed the accuracy of endocarditis diagnostic codes. Sensitivity and PPV of the ICD-9 codes equivalent to those used here (**Table 16**, **Table 17**) were higher than in my study (0.94/0.94[228], 0.90/0.78[257], 0.70/0.70 Leeds). Both the US[14] and Canadian[257] studies also identified the poor predictive value of 'Endocarditis, valve unspecified' (ICD-9 424.9, corresponding to code I38), though they did not identify the underlying cause (incorrect guidance in the coding manual). Previous meta-analyses of coded data to identify healthcare-associated-infections have noted moderate sensitivity in detecting *Clostridium difficile* infection (pooled sensitivity 76%, specificity 99%) and surgical site infections (sensitivity 81% specificity 97%)[258]. A US study of sepsis coding compared to sepsis objective clinical criteria found that admissions with sepsis codes had increased, which was not reflected in incidence of admissions meeting sepsis clinical criteria, possibly due to changes in coding behaviour[259].

There is one other large-scale infective endocarditis study that used direct microbiological data rather than administrative diagnostic codes was via three population-based surveys undertaken at different time periods[241]; it also found no increase in the proportion of cases caused by streptococci. A much smaller study of 106 admissions with infective endocarditis

linked with corresponding blood cultures suggested the proportions of causative organisms were similar in coded and microbiological data[235], similar to my results.

Supplementary codes in particular may be more susceptible to changes in coding behaviour, such as incentivisation to record more secondary codes[193,194] (so-called 'coding depth') or specific organisms, or availability and expertise of coding staff. However, analysis of incidence of endocarditis attributed to specific organisms differs from analysis of proportions of endocarditis with an organism code that are attributed to specific organisms. The previous study using English HES data[223] found that the proportion of endocarditis cases with any supplementary causal organism coded increased over time, particularly before 2009. Given my observations that trends in streptococcal endocarditis based on use of supplementary coding may not match those based on clinician-recorded cases, my study supports the view that using these codes is unlikely to give meaningful information on the incidence of organism-specific endocarditis. However, where changes are driven by coding depth (i.e. more codes are recorded over time, but with no specific preference for particular secondary/supplementary codes over others), proportions should be relatively unaffected.

In terms of causative organisms, this study's finding that the most common species were Staphylococcus spp. and Streptococcus spp. is similar to other studies. Oxford blood culture and matched admissions data estimated a much larger percentage of culture negative cases compared to Leeds clinician-recorded data (28% vs 7% culture negative respectively), though both numbers are in keeping with previous estimates (2-31%)[260,261]. The most likely cause of this difference is probably imperfect case identification using our administrative information algorithm (all codes except I38, short stays and readmissions removed) which had a PPV of 0.78, leading to inclusion of a number of admissions which did not represent a case of endocarditis. Additional explanations may be more community antibiotic therapy in Oxford prior to hospital presentation, leading to culture negative cases.

4.4.5 **Implications for electronic health record study design in endocarditis**

My work suggests that studies investigating endocarditis using electronic health record data should not use the "I38: Endocarditis: valve unspecified" code in the secondary position, further supporting the findings of Toyoda *et al*[228]., since coding protocols allows it to be assigned to admissions featuring nonspecific valve disorders entirely unrelated to endocarditis. Of note, most previous studies of endocarditis incidence did not use this code and are not affected by the issue, although at least two studies have used it[222,246] (**Table 17**).

Table 20 and **Table 21** show clearly the trade-offs between sensitivity, specificity and PPV in any coding algorithm. How these are balanced may depend on the aims of any particular study. If the goal is to maximise sensitivity to assess overall incidence levels, then inclusion of secondary codes, and potentially manual review of secondary codes with low positive predictive value, may be required, or risk missing 25-50% of cases. Where manual review is impractical, then identifying the highest sensitivity that maintains reasonable specificity and/or PPV may provide the best balance. It is important to note that whilst maximising PPV alone may appear attractive, a very strict rule can achieve high PPV whilst missing most true cases (low sensitivity), underestimating incidence and with an uncertain impact on trends. Overall I consider that using all codes except I38 secondary provides a good balance between PPV and sensitivity (**Figure 16**) in these datasets.

4.4.6 **Clinical and policy implications**

Regarding the clinical concern that infective endocarditis increased in England[223] and the US[244] after changes in antibiotic dental prophylaxis around 2007, my work suggests that the major studies examining endocarditis incidence have not used any poorly-predictive codes,

but that the algorithms used could nevertheless have overestimated incidence trends by including short admissions/readmissions. In particular, moves to reduce length of stay in English hospitals have been accompanied by parallel increases in readmissions over the last decade[262] with uncertain impact on epidemiological analyses like these.

Given the discrepant findings of electronic health record studies in this area to date (**Table 16**), work to definitively quantify the efficacy of dental prophylaxis in preventing endocarditis may require a national registry of disease to be established, as previously suggested. However, these are not without their drawbacks and concerns about data quality, and require significant resources. Alternatively, despite the significant resources required, it may be that efforts to set up a large-scale individually randomised controlled trial will ultimately be required to test the benefits of antibiotic prophylaxis. Given the results from my preceding Chapters, I would note that it is essential that any such trial also tries to capture microbiological and resistance outcomes.

4.4.7 Implications for electronic health record study design in general

My study illustrates clearly that using diagnostic codes which appear to represent a disease entity based on their code title without any attempt to validate these codes to clinically confirmed cases can lead to very large errors if done incautiously. This has relevance beyond the field of endocarditis, and is applicable to any study conducted using diagnostic codes to assess patterns of disease. Without deduplication and careful code choice, more than half the codes assigned can represent not cases, but readmissions, investigations where the presumptive diagnosis is later ruled out, and past histories. A diagnostic code most definitely does not necessarily equal a clinical case. Importantly, this does not generally suggest problems with clinical coding per se, only that the current clinical coding process has

different goals to epidemiology, being primarily for reimbursement and recording of hospital activity, rather than clinical diagnoses.

Secondary codes can be susceptible to changes in coding behaviour, depending on the disease entity, including measures to increase quality as well as 'up-coding' (choosing the code worth the most) or 'coding inflation' (where multiple secondary codes are used to increase reimbursement), which have been reported in UK and other healthcare settings using these systems[193,194,263]. However, studies that aim to maximise inclusion of possible cases should not automatically disregard these secondary codes, as a substantial proportion of confirmed clinical cases may only receive a secondary code, as in my endocarditis examples.

Recommendations for conducting observational studies using routinely-collected health data already exist[264] and include detailing validation study methodology or providing references for this. In studies which use a very large selection of diagnostic codes, it may not be possible to validate every code, but at minimum, diagnostic codes that occur most commonly should be monitored over time by centre, and unexpected changes discussed with both coding and clinically trained staff. Additionally, studies using coding would benefit from a statement by authors which justifies the chosen coding strategy based on available data, and highlights the limitations of their approach. Any clinical decisions made using diagnostic code-based analyses should also formally consider whether robust validation of coding has been performed and review justification for the chosen strategy.

Finally, my study suggests more work is needed to explore novel methods of improving case identification using electronic health records, such as improving data linking between admissions and microbiology results[211], using natural language processing methods[197], machine learning approaches[198], or healthcare process modelling[265], and supporting efforts to share, evaluate, and refine these methods[266].

4.4.8 **Implications for studies of antibiotic prescribing and resistance**

This study suggests that even when there is a well–recognised gold standard for the diagnosis of an infection, which has a clearly recognisable spelling, using diagnostic codes to identify cases of this infection still has limitations. In addition, using secondary/supplementary organism codes to identify infectious due particular bacteria has to be done with caution. Where possible, objective microbiological data would be superior, being less affected by the extra levels of human data entry error, and ambiguity as to whether the code represented a new occurrence of infection, or a past history.

4.5 **CONCLUSION**

This study comprehensively evaluated the accuracy of clinical coding of infective endocarditis in two UK centres. It highlights that diagnostic codes were never intended for observational epidemiology, and "mission creep" in their use requires validation against other sources of data rather than the assumption that verbal descriptions are clinically meaningful. Their findings cannot be seen as definitive or replacing other research methodologies. They are useful as a relatively resource-light method of assessing issues that demand closer attention where possible, or studying issues where other research methods are infeasible. The study should serve as a learning point for anyone wishing to use diagnostic codes to assess patterns of disease, and emphasises the need for improvements in how clinical diagnoses are defined using routinely collected data.

5 CHAPTER 5: RISK FACTORS FOR BETA-LACTAM RESISTANCE IN BLOODSTREAM INFECTIONS DUE TO ENTEROBACTERIACEAE IN OXFORDSHIRE: A CASE CONTROL STUDY

5.1 INTRODUCTION

Beta–lactam antibiotic resistant Enterobacteriaceae are rapidly becoming one of the most pressing challenges in public health. Enterobacteriaceae can rapidly develop resistance due to horizontal gene transfer, and can colonise and spread through multiple environments[267]. *E. coli* is the leading cause of bloodstream infections in the UK[268] and high-income countries[269]. Hospital and community medicine is highly reliant on beta-lactam antibiotics[268,270], as they are effective and have few side effects, but resistance to these agents is associated with poorer clinical outcome[271]. The World Health Organisation has assigned Enterobacteriaceae resistant to beta-lactam antibiotic classes (3rd generation cephalosporins and carbapenems) critical priority pathogen status for these reasons.

5.1.1 Antibiotics as a risk factor for resistance in Enterobacteriaceae bloodstream infections

5.1.1.1 *Review of existing literature and identification of non-antibiotic and antibiotic risk factors from previous studies*

To assess the existing knowledge on the antibiotics, and other risk factors, associated with resistance in Enterobacteriaceae, and inform my study design and data collection strategy, I searched the PubMed database from 1990 to 2019 using combinations of the keywords "resistant" "resistance" "Enterobacteriaceae" "E. coli" "Escherichia" "Klebsiella" "bloodstream" "infection" "antimicrobial" "antibiotic" "exposure", placing no restrictions on language. I also hand-searched bibliographies of retrieved articles for additional references.

Studies were included if they were case-control studies or cohort studies with a resistant infection case group and a susceptible infection or no infection control group, and assessed risk factors associated with resistant bloodstream infection in Enterobacteriaceae, *E. coli* or *K. pneumoniae* (with or without other organisms). Previous studies of bloodstream infections that have investigated associations between prior antibiotic use and risk of resistant infection, particularly for beta-lactams, are summarised in

Table 24.

5.1.1.2 ***Antibiotic risk factors***

Of case-control studies, six studies found associations between beta-lactam resistance and cephalosporin use[272-277], two studies found associations between beta-lactam resistance and prior quinolone exposure[277,278], one study found association between carbapenems and beta-lactam resistance[279], and one study beta-lactam resistance and co-trimoxazole exposure[276]. Associations between longer duration of prior antibiotic therapy and resistance have not been identified in bloodstream infections, only in a few limited studies of upper-respiratory tract infections[104] and ventilator-acquired pneumonia[97]. Of three cohort studies, none looked at specific antibiotic exposure or duration of therapy[280-282]. The most common timescale studied in terms of prior exposure was the preceding 30 days/1 month (6 studies), with the longest duration being the preceding 12 months, and the shortest duration being 2 weeks.

The associations between beta-lactam resistance and use of different classes of antibiotics is intriguing. Indeed, assuming that use of a particular class is the most potent selector for resistance to that class may be an oversimplification, and alternative, stronger relationships may be more relevant. Cross-resistance has previously been demonstrated in Enterobacteriaceae, for example where trimethoprim exposure selected for beta-lactam resistance as the relevant genes were co-carried on the same genetic element[52], and

associations between trimethoprim use and beta-lactam resistance have been demonstrated on a population level previously[52,162]. Alternatively it may be that selective effects are modified by the concentrations of antibiotics that reach the gut, a major site of resistance selection for the Enterobacteriaceae[127], due to method of administration or pharmacodynamics profile[128,283].

Therefore it is of interest to study associations between multiple antibiotic classes, as well as route of administration, and beta-lactam resistant infections. For example, if co-selection is a significant phenomenon, it is possible that well-meaning attempts to change the antibiotic formulary away from beta-lactams may actually have no effect on resistance selection, if alternative antibiotics such as fluoroquinolones and trimethoprim/sulphamethoxazole also select for beta-lactam resistance. Equally, if oral administration of antibiotics leads to higher gut concentrations and more selection for resistant Enterobacteriaceae in the gut, current stewardship interventions aimed at reducing intravenous antibiotic use may inadvertently increase, rather than decrease, resistance selection. Finally, it is important to explore the associations between duration of therapy and resistance, given the efforts being made to reduce the length of antibiotic courses – will this have any effect on antimicrobial resistance?

5.1.1.3 *Non-antibiotic risk factors*

Other risk factors identified in previous studies include hospital exposure, duration of exposure, age underlying chronic disease, recent surgery, care facility exposure, steroid use, admissions to haematology/oncology units, indwelling devices including urinary catheters, female and male sex, and, previous infection or colonisation with resistant organisms, (summarised in

Table 24), which helps inform my study design and data collection.

It is worth considering multiple potential confounding effects. For instance, older, more comorbid, patients will be more likely to both receive antibiotics and be exposed to resistant pathogens through exposure to healthcare environments where their prevalence is higher.

5.1.1.4 ***Study design considerations***

With the aim of identifying the antimicrobial exposure associated specifically with resistant infection (as opposed to infection as a whole) I will compare infection with a resistant vs susceptible isolate. Theoretically I could have considered a cohort design, whereby I identified a time zero and followed individuals forward in time to assess whether different risk factors and antibiotics prior to time zero affected the incidence of infections with resistant vs susceptible isolates. However, one major challenge is identifying a relevant time zero given that patients are at risk throughout life, although this risk differs substantially by age. Reflecting my search above, I therefore chose to perform a case-control study of bloodstream infection due to *E. coli* or *K. pneumoniae* comparing patients with a beta-lactam-resistant isolate to patients with a beta-lactam-susceptible isolate, using linked electronic health record and microbiology data of patients in Oxfordshire area, using multivariable models to adjust comparisons of prior antibiotic use for relevant confounders. With detailed hospital prescribing information available in these databases from late 2015, I assess individual classes of antibiotic, route and duration of therapy as risk factors for resistance. Based on the previous literature, I chose to conduct the analysis based on exposure to antibiotics in the prior month (most commonly assessed in previous studies), and also in the prior year.

Table 24: Summary of previous studies of bloodstream infection and risk factors for resistance

Authors	Study population	Comparison	Risk factors	Antibiotic risk factors
Case-Control Studies: Comparison of resistant vs susceptible infection				
Balazs Ivady et al[272]	135 gram-negative bloodstream infection episodes in children in Hungary 2010-2011 (29 *E. coli*, 26 *Klebsiella* spp)	45 with multi-drug resistance (MDR) (resistant to at least 3 classes of antibiotic)[284], 90 non-MDR	Older age, admission to haematology/oncology	Prior cephalosporin treatment (preceding 30 days)
Barrera-Vargas et al[285]	88 patients with bloodstream infection and Systemic Lupus Erythematosus (SLE) 2001-2012 Mexico	44 with ESBL *E. coli*, Pseudomonas or MRSA; 44 with susceptible *E. coli* or MSSA	Steroid use, low blood complement (C3) levels, previous hospitalisation	Not studied
Van Aken et al [286]	210 patients with *E. coli* bloodstream infection 2011-2012 Sweden	70 ESBL, 140 non-ESBL isolates	Previous culture of ESBL-producing bacteria	Prior antibiotic treatment (preceding 6 months)associated with ESBL status in univariate, but not multivariate, analysis
Wu et al[273]	182 patients with *E. coli* bloodstream infection 2005-2007 Taiwan	91 ESBL, 91 matched susceptible isolates	Urinary catheterisation, hospital-acquired infection	Antimicrobial use (preceding 30 days), cephalosporins
Fernandez Quirante et al[287]	112 patients with *E. coli* or *K. pneumoniae* bacteraemia Spain 2000-2006	53 patients with ESBL, 159 matched controls (on organism, age, severity)		More than 2 classes of antimicrobial (preceding 90 days)
Pena et al[288]	81 *E. coli* bacteraemia cases 1998-99 in Spain	27 fluoroquinolone resistant, 54 susceptible	Urinary tract infection, underlying chronic disease	Prior fluoroquinolone use(preceding 3 months)
Nasa et	95 *E. coli* and *K. pneumoniae*	73 ESBL, 12 non-ESBL	Transfer from other	Prior antibiotic use (preceding

Authors	Study population	Comparison	Risk factors	Antibiotic risk factors
al[289]	positive blood cultures in patient admitted to an ICU in India		hospitals	90 days)
Du et al[274]	85 patients with *E. coli* or *K. pneumoniae* bacteraemia in a Chinese tertiary centre 1997-99	23 ESBL, 62 non-ESBL		Prior treatment (preceding 2 weeks) with 3rd generation cephalosporins
Zaoutis et al[275]	140 patients with *E.coli* or *K. pneumoniae* bloodstream infection in a US centre 1999-2003	35 ESBL, 105 non-ESBL	Female, steroid use in previous 30 days	Exposure to cephalosporins, (preceding 30 days), exposure to an extended-spectrum cephalosporin in (preceding 30 days)
Gomez Rueda et al[279]	122 patients with *K. pneumoniae* bloodstream infection presenting to a hospital in Colombia	61 with carbapenem resistance, 61 with no carbapenem resistance	Colonisation with carbapenem-resistant strains	Exposure to carbapenems.(preceding 14 days) Specifically no association with quinolone exposure found
Lim et al[290]	360 patients with a bloodstream infection	MDR (180 Enterobacteriaceae, MRSA with >3 classes, or Vancomycin Resistant Enterococcus (VRE)) vs 180 matched controls with same genus, but susceptible, organism	Resident in a long term care facility, home wound care, immunosuppression, recent surgery	Prior exposure to antibiotics (preceding 3 months). No significant association was seen between individual antibiotic classes and resistance
Von Baum et al[291]	314 hospitalised patients 1999-2001 with a bloodstream infection with MRSA, Candida spp, ESBLs or VRE	20 with ESBLs alone or with other MDR pathogens, VRE candidaemia vs 294 with other pathogens but without ESBLs	ESBL infection associated with burns, tracheostomy and dialysis	Not studied
Freeman et al[277]	88 patients at a New Zealand tertiary hospital 2003-2007 with a blood culture growing Enterobacteriaceae	44 ESBL vs 44 non-ESBL Enterobacteriaceae, matched by onset location, peripheral/central line collection, and species	Previous ESBL colonisation	Fluoroquinolone exposure, 1st generation cephalosporin exposure (preceding 12 months)

Authors	Study population	Comparison	Risk factors	Antibiotic risk factors
Zerr et al[276]	1204 children/young adults <22 years with *E. coli* or *K. pneumoniae* isolates from normally-sterile sites	210 ESBL isolates and 94 AmpC producers vs 900 susceptible organisms	Male, previous hospitalization, indwelling device, underlying medical conditions	ESBL: Antibiotic exposure (preceding 30 days), plus 3rd generation cephalosporins, broad-spectrum beta-lactams and co-trimoxazole exposure. AmpC producers: not associated with prior antibiotic use except 3rd generation cephalosporins.
Case-Control Studies: Comparison of resistant infection and non-infected controls				
Pena et al[278]	103 hospitalised patients with ESBL *E. coli* bloodstream infection 1996-2002	103 ESBL vs matched uninfected controls	Female, nasogastric feeding	Prior antibiotic use (preceding 3 months), beta-lactam use specifically
Gallagher et al[292]	308 patients with *K. pneumoniae* bloodstream infections	111 isolates with 3rd generation cephalosporin and carbapenem resistance, 43 with carbapenem resistance, 154 matched controls with no bloodstream infection	Length of stay	Antibiotic use (preceding 90 days)
Rodriguez-Bano et al[293]	Inpatients with a positive blood culture in 13 Spanish hospitals 2004-2006	96 ESBL *E. coli* bloodstream infection, 186 matched controls with no infection	Type II diabetes, length of stay, previous transplant	Prior beta-lactam use during same admission (mean 24 days)
Cohort studies				
Cardoso et al [280]	Prospective study of 1035 patients with infection presenting to tertiary care centre in Italy 2008-2009, 439 had microbiologic documentation, mixture of bloodstream and other site infections (number with bloodstream infections not	104 MDR gram-negative infections compared to 171 non-MDR infections (41 patients with ESKAPE and 123 non-gram-negative-MDR infections not included in MDR-Gram-negative analysis)	Age, hospitalisation in prior year	Prior antibiotic use (preceding month) significant on univariate but not multivariate analysis

Authors	Study population	Comparison	Risk factors	Antibiotic risk factors
	specified)			
Cordery et al [282]	Retrospective cohort study of all patients admitted to a UK intensive care unit 2004-2006 with *E. coli* or Klebsiella spp. bloodstream infection	16 ESBL compared to 39 ESBL negative infections	Prior positive urine culture with "similar organism"	ICU antibiotic use (during current ICU stay, variable duration, time not given) not significant on univariate or multivariate analysis
Rosa et al [281]	Prospective study of 307 patients with febrile neutropaenia being treated for cancer in a Brazil haematology ward	38 resistant bloodstream infections (10 *E.coli*, 3 *K. pneumoniae*) compared to 269 non-resistant infections (44 *E. coli* 13 *K. pneumoniae*)	Age, duration of neutropaenia, presence of indwelling central venous catheter	Antimicrobial treatment (preceding 30 days) not associated with resistance in univariate or multivariate analysis

Note: Multi-drug resistance (MDR); Vancomycin Resistant Enterococci (VRE); Methicillin Resistant Staphylococcus Aureus (MRSA), Methicillin Susceptible Staphylococcus Aureus (MSSA), Extended Spectrum Beta-Lactam Resistant (ESBL)

5.2 STUDY DESIGN: INFLUENCES OF PREVIOUS WORK

5.2.1 Case control study addresses low incidence of resistant infection in my study population

My work in Chapter 2 explored antibiotic prescribing in acute, unselected medical admissions. A key limitation of that study was that I did not look specifically at risk of future resistant infection, just at immediate clinical outcomes. This is because the relatively low incidence of resistant infection in my study population (297 admissions) meant that the study lacked power to identify anything but very large associations. Whilst I was able to look at a larger dataset of 1 year of admissions and mortality and length of stay data (47,585 admissions), this had neither detailed antibiotic exposure data nor detailed information on what types of resistant infection was encountered. To address the issue of low incidence of the studied outcome (resistant infection), I used a case-control study for this Chapter to enable me to investigate associations between antibiotic use and resistant infections despite the low incidence.

5.2.2 Electronic prescribing data now allows larger studies without time consuming manual collection

Since the completion of Chapter 2, electronic prescribing was introduced to the hospital (from late 2015), a project that I was involved in personally as a member of the e-prescribing working group. This meant that electronic antibiotic data has become available on an individual level, with the entire hospital Trust switching to electronic recording from 2016 onward. This resource was not available when I completed Chapter 2. Through database linkage, this means that I am able to look at all hospital antibiotic exposure from 2016 onwards in individuals with infections.

5.2.3 **Defining 'broad-spectrum' vs 'narrow-spectrum' antibiotics - what should I be comparing?**

In Chapter 2, I compared broad- vs narrow-spectrum antibiotic use between an infectious diseases-trained physician (IDP) and other physicians, showing the IDP used less broad-spectrum antibiotics. This was of relevance given one key question of my DPhil is whether reducing broad-spectrum antibiotic use may have any impact on resistance.

However, as I briefly covered in my introductory Chapter 1, there is no universal consensus for what constitutes a broad-spectrum antibiotic, being defined loosely as an antibiotic which acts against both gram-positive and gram-negative bacteria, or acts against a wide range of bacteria. Some have even called for the term to be scrapped, viewing it as inherently unhelpful[117]. When focusing on beta-lactams specifically, there is no one authority for the definition of broad spectrum, and many different views exist. If one goes by the definition based on gram-positive and gram-negative activity, penicillin is considered narrow-spectrum as it has no gram-negative bacillus activity (it does have activity against gram-negative cocci such as meningococcus), whilst ampicillin and amoxicillin are technically broad-spectrum as they have gram-negative bacillus activity. However there are many publications view and analyse amoxicillin as a narrow-spectrum beta-lactam[294,295], whilst co-amoxiclav (amoxicillin with a beta-lactamase inhibitor, clavulanic acid) is analysed as broad-spectrum. Indeed, many stewardship activities in the UK focus on reducing use of co-amoxiclav or piperacillin/tazobactam (another beta-lactam/beta-lactamase combination), and encouraging amoxicillin use. In Chapter 2, I defined broad-spectrum antibiotics in line with other publications from my research group members (as a beta-lactam penicillin/beta-lactamase inhibitor, cephalosporin, quinolone or carbapenem)[270] which reflected the attitudes and policies at the time in the Oxford hospitals where the study was done.

In 2017 the World Health Organisation introduced a new classification of antibiotics created by expert consensus – grouping antibiotics as Watch, Access, or Reserve[119] (**Table 25**) (recently updated in July 2019[118], 2017 version used in this Chapter). Access antibiotics "should be widely available, affordable and quality-assured". Watch antibiotics "includes antibiotic classes that have higher resistance potential and so are recommended as first or second choice treatments only for a specific, limited number of indications. These medicines *should be prioritized as key targets of stewardship programs and monitoring*". Reserve antibiotics "should be treated as "last resort" options". Countries are encouraged to develop their own versions of this classification, and the UK version has been presented as an abstract[296] (and is very similar to the 2019 revision). The most major difference from the point of this analysis is that co-amoxiclav is viewed as an 'Access' antibiotic by the WHO, but a 'Watch' antibiotic in the 'stricter' UK version. (Amoxicillin is an 'Access' antibiotic in both.)

In this subsequent analysis, I will investigate whether there any evidence that antibiotic stewardship activities *at any individual study site* may have any impact on reducing resistance, i.e. any evidence that UK 'Watch' list antibiotics are more associated with resistance in Enterobacteriaceae, compared to 'UK access' list antibiotics, and specifically access vs watch beta-lactams. I will classify beta-lactams on the UK 'Watch' list as broad-spectrum, and those on the 'Access' list as narrow-spectrum, i.e. will treat co-amoxiclav as 'Watch'.

If so, this would provide some support for the classifications. However I will also investigate spectrum of activity, specifically dividing beta-lactams into those with and without activity against (gram-negative) Enterobacteriaceae.

Table 25: Beta-lactam antibiotics and classification according to spectrum

Name	Activity	Broad or narrow (>1 class) as in Chapter 2	WHO definition	UK interpretation of WHO definition
Penicillin	Gram-positive	Narrow	Access	Access
Flucloxacillin Methicillin	Gram-positive	Narrow	Access	Access
Ampicillin Amoxicillin	Gram positive and limited gram negative	Broad	Access	Access
Co-amoxiclav (amoxicillin/clavulanic acid)	Gram positive and more gram negatives	Broad	Access	Watch
Cefalexin	Gram positive and limited gram negative	Broad	Access	Watch
Other 1st and 2nd generation cephalosporins	Gram positive and some gram negative	Broad	Access or watch	Access or watch
Ceftriaxone and other 3rd generation cephalosporins	Gram positive, gram negative and Pseudomonas	Broad	Watch	Watch
Piperacillin/tazobactam	Gram positive and more gram negatives including Pseudomonas	Broad	Watch	Watch
Carbapenems	Gram positive, gram negative and Pseudomonas	Broad	Watch	Reserve
Aztreonam	Gram positive and gram negative	Broad	Reserve	Reserve

5.2.4 **STUDY DESIGN – INFLUENCES FROM CHAPTERS 4 AND 5**

5.2.4.1 ***Use of diagnostic codes***

In Chapter 3, I found that using diagnostic codes assigned at discharge was a relatively robust method of estimating comorbidity at point of admission. As such, I will continue to use this method to adjust for confounding factors in this piece of work, though I will also consider other methods of estimating comorbidity, discussed below.

In Chapter 4, I found that data from diagnostic codes assigned to admissions on infections and organism were of variable quality. In particular, using diagnostic coding to identify patients with a diagnosis of infection was subject to major pitfalls - these patients may have had the infection investigated and excluded, or been readmitted with a complication of the original infection. Coded data on organism, and also on resistant infections, was variably recorded. For confirmed *Staphylococcus* spp. endocarditis infections, 68% had a staphyloccoccus diagnosis code and 28% had no organism code. For confirmed *Streptococcus* spp. endocarditis, 58% had a streptococcus code. 6% and 4% respectively of Staphylococcal or Streptococcal coded admissions had a code representing the wrong organism.

The Infections in Oxfordshire Research Database (IORD)[211] has linked microbiology test results, which can be used to identify microbiologically confirmed infections directly. However culture data does not necessarily differentiate harmless colonisation from infection. For instance, isolation of *E. coli* from urine samples can occur in a patient with no urinary symptoms, and this may not be considered pathological or sign of an 'infection'. The same would apply to skin or faecal swabs. However bacterial isolation from blood cultures – a usually sterile site - would, almost without exception, be considered a pathological finding. As such, it is reasonable to take the view that the isolation of bacteria from blood cultures means that there was a true infection, without the need to use diagnostic coding data.

Additionally, the direct microbiology data gives me detailed information on the organism and resistance antibiogram, without relying on the diagnostic codes.

5.2.4.2 *Using multiple data sources to try and establish better identification of disease entities to use as confounders*

As previously stated, in Chapter 4 I noted it was not infrequent for diagnostic codes for endocarditis to be assigned to cases where endocarditis was investigated and ruled out. This is likely to be an issue beyond endocarditis alone. The IORD database contains data on ward movements, such that certain disease entities, such as cancer, can be assessed based on both diagnostic codes data and patient stays on the cancer/haematology wards.

5.2.4.3 *Assessing alternative methods of using coding data to measure comorbidity that does not rely on assuming clinical codes are an indicator of disease, such as the hospital frailty score*

The hospital frailty score has recently been proposed as a method of assessing patient frailty using diagnostic coding[297]. In brief, the researchers identified disease entities associated with frailty such as dementia, identified associated codes, and then studied which other diagnostic codes were commonly used in patients with pre-identified frailty disease-related codes. These associated codes were commonly entities such as ‘delirium’ or ‘acute confusional state’ and are effectively measures of how frail patients interact with the healthcare system. They created and validated a hospital frailty score based on these associated codes which was strongly associated with clinical frailty scores such as the Rockwood[298]. I intend to investigate whether this score can be used as a measure of frailty, itself a significant risk factor for infection, and hence I would hypothesise, resistant infection.

5.2.4.4 *Assessing alternative methods of calculating comorbidities based on coding data from linked, or previous, admissions*

Current accepted methods for calculating the Charlson score as a measure of comorbidity use the 'dominant' admission – the first episode of the hospital admission spell linked to the presentation with a disease (unless the first episode has a nonspecific symptom-based 'R' code, in which case the second episode is used, unless this too contains an 'R' code)[177]. However these assigned codes will represent both comorbidities present prior to presentation, and conditions as a result of the presenting disease. For instance, a patient who presents with sepsis and renal failure due to severe disease will receive codes for both the infection, and the sequelae. In Chapter 3, I investigated this issue in detail. However, one might hypothesise that more severe, resistant infections may also cause more renal failure, and hence using the 'renal failure' codes to control for comorbidity as a risk factor for resistant infection may thus be erroneously adjusting for a consequence of the outcome. This may have been less problematic in my audit in Chapter 3 which was of unselected acute admissions, rather than in this study where I am focussing on resistant bloodstream infections as cases.

In this Chapter, I therefore used two methods of calculating the comorbidities associated with the Charlson score, and the Charlson score itself – using all primary and secondary codes from one year of admissions strictly prior to the presentation with infection (ie discharged before the admission with the positive blood culture), and using the codes from the dominant admission linked in time to the infection as currently recommended. I will investigate the strength of association between each measure and resistance in both univariate and multivariate analyses.

5.2.5 **Research aims**

Based on the factors discussed above, the primary aim is to assess the association between prior hospital exposure to multiple different antibiotic classes in the prior month (and then

subsequently in the prior year) and beta-lactam resistance in *E. coli* and *K. pneumoniae* bloodstream isolates in Oxfordshire. I will assess this both in terms of any exposure, and subsequently a quantitative analysis to look at whether longer courses are associated with resistance. I will also look for any differences in effect between oral and intravenous preparations, and consider the different definitions of broad-spectrum beta-lactams. The secondary aim is to assess different methods of calculating the Charlson score and frailty score, for use in risk adjusted analyses of infections.

5.3 **METHODS**

5.3.1 **Setting**

In this case control study, I used routinely collected, anonymised electronic health records from IORD[211]. To recap, IORD contains anonymised records of all admissions from 1997 onwards to the Oxford University Hospitals NHS Foundation Trust (OUH), together with linked patient demographic data, microbiology and pathology test results. The OUH is a teaching hospital with three associated tertiary care centres, serving a population of 655,000 with 1465 beds[299] and is the only provider of acute and specialist services in the region. The OUH laboratory processes microbiology samples from the Oxfordshire region for primary care facilities and community hospitals, as well as the OUH itself.

5.3.2 **Study design**

All adult (18 years or older) patients with a blood culture taken between 00:00 1st January 2016 – 23:59 31st December 2017 and growing *E. coli* or *K. pneumoniae* were included. Cases were defined as patients with positive blood cultures with resistance to beta-lactam antibiotics (as defined below), including the first resistant isolate per-patient only as the case

so that the antibiotic exposure factors reflected the minimum that could be associated with resistance. Controls were patients with positive blood cultures but no resistance to beta-lactam antibiotics in any isolate during the study period; the last susceptible isolate was included as the control to maximise antibiotic exposure in patients with susceptible isolates. Culture and susceptibility testing was performed by the OUH microbiology laboratory in accordance with standardised laboratory procedures[250], using microbroth dilution (BD Phoenix Automated Microbiology System). It is worth noting that issues have been raised with the reproducibility of susceptibility testing for co-amoxiclav in Enterobacteriaceae, especially for intermediate-susceptible phenotypes, possibly due to inducible resistance mechanisms (Vihta et al[54] and Davies et al[300]).

5.3.3 **Definitions**

Beta-lactam resistance was defined as resistance to any of the following antibiotics on susceptibility testing: co-amoxiclav, cephalexin, cefuroxime, ceftriaxone, ceftazidime, cefradine, cefepime, cefotaxime, cefoxitin, ceftazidime/avibactam, ceftolozane/tazobactam, piperacillin/tazobactam, imipenem, meropenem, ertapenem, and aztreonam. The routine laboratory also routinely tested for resistance to gentamicin, ciprofloxacin, trimethoprim. I did not consider amoxicillin or ampicillin resistance as defining beta-lactam resistance because *K. pneumoniae* is almost universally resistant, and *E. coli* widely resistant, to these drugs (which are both considered 'Access' antibiotics).

5.3.4 **Primary exposure**

The primary exposure was defined as hospital antibiotic administration of a given antibiotic in the month, or year, prior to the blood culture sample being taken, according to class and

method of delivery (oral or intravenous). I grouped all antibiotics prescribed into classes, which were subsequently reviewed by three Microbiology/Infectious Diseases trained clinicians to reach consensus (**Table 26**). Analysis was performed based on exposure to any antibiotic in a given class in the prior year or month preceding the bloodstream infection.

Table 26: Antibiotic classes and drugs considered in analysis

Class	Drugs
Beta-lactams on UK 'Watch' list (or Reserve list)	*Co-amoxiclav Temocillin Piperacillin/Tazobactam Aztreonam *Cefalexin Pivmecillinam Meropenem Imipenem Ertapenem Ceftriaxone Ceftazidime Ceftolozane Cefuroxime Cefotaxime Cefoxitin
Beta-lactams on UK 'Access' List	Ampicillin Amoxicillin Flucloxacillin Phenoxymethylpenicillin Benzylpenicillin
Beta-lactams with gram-negative activity	Ampicillin Amoxicillin *Co-amoxiclav Temocillin Piperacillin/Tazobactam Aztreonam *Cefalexin Pivmecillinam Meropenem Imipenem Ertapenem Ceftriaxone Ceftazidime Ceftolozane Cefuroxime Cefotaxime Cefoxitin

Class	Drugs
Beta-lactams with no gram-negative activity	Flucloxacillin Phenoxymethylpenicillin Benzylpenicillin
Quinolone	Ciprofloxacin Moxifloxacin Levofloxacin
Aminoglycosides	Gentamicin Amikacin Tobramycin
Anti-folate antibiotics	Trimethoprim Co-Trimoxazole
Cephalosporins	Ceftriaxone Ceftazidime Ceftolozane Cefuroxime Cefalexin Cefotaxime Cefoxitin
Tetracyclines	Doxycycline Lymecycline Minocycline Oxytetracycline Tetracycline
Carbapenems	Meropenem Imipenem Ertapenem
Anti-anaerobic	Metronidazole Fidaxomicin Vancomycin enterically

*on WHO Access list

5.3.5 **Variables**

Based on the factors considered in previous studies, and my own previous analyses, variables assessed as potential confounders were, in the prior year (see following paragraphs for definitions):

- number of admissions, emergency admissions, complex admissions
- previous admission under surgery, under medicine, under haematology/oncology, to intensive care units

- previous catheter
- previous evidence from diagnostic codes of ischaemic heart disease, congestive cardiac failure, dementia, diabetes, diabetes complications, liver disease, severe liver disease, peripheral vascular disease, peptic ulcer disease, cancer, metastatic cancer, paraplegia, renal impairment, HIV diagnosis (based on the International Classification of Diseases Version 10 (ICD-10) diagnostic codes assigned to prior episodes, using relevant codes from Charlson coding algorithms[204])
- number of procedures
- previous orthopaedic, gastrointestinal, genitourinary, skin/soft tissue, vascular, endoscopic, cardiothoracic, or other surgical procedures
- demographics (age, sex, ethnicity) and index of multiple deprivation

One important caveat about all factors is that they are based on presence of different codes in the underlying electronic data; hence there is no "missing data" by definition. If data are genuinely missing in the electronic data source, I have no way to identify this.

5.3.6 Identification of care teams and specialities

For specialties which managed patients in diverse locations, such as general medicine and general surgery, consultant specialty codes were used to identify admissions under general medicine (code 300) or surgery (100, 101, 110, 120, 130, 140, 145, 150, 160, 170). For specialties which manage patients solely in dedicated units (intensive care, haematology and oncology), patient identification was performed based on ward occupancy data.

An admission was defined as a hospital provider spell ("the total continuous stay of a patient [..] on premises controlled by a Health Care Provider") according to NHS Business definitions[255]. Each spell comprised a number of consultant episodes, each with a primary ICD-10 code (the main condition treated or investigated) and up to 20 secondary codes for

other relevant conditions and/or supplementary codes, e.g. reflecting organisms isolated (subsequently denoted ‘secondary codes’). Emergency admissions were defined as having a non-elective admission source (admission source code other than 11, 12 or 13). Complex admissions were defined as having 2 or more consultant episodes within a spell.

The most relevant admission was chosen using time-based criteria. Firstly, any admission which overlapped with the collection date/time of the bloodstream isolate was chosen. If this did not exist, then an admission up to 48 hours after the bloodstream isolate collection date/time was chosen (in case the culture was taken in the emergency department, community or outpatient setting, and the patient was subsequently admitted). 411/993 (41%) patients had a blood culture taken before time of admission, but only 19/993 (2%) patients had a blood culture taken more than 24hrs before admission.

5.3.7 **Catheter identification**

There are still no dedicated hospital codes for the catheterisation procedures that are commonly used, and insertion is often poorly recorded in the patient hospital records. To identify patients who had had a catheter in the prior year, I identified any patients with a catheter-specimen urine sent for microbiology testing. Given that many patients with a catheter may not have had a specimen sent, this will under-identify true catheter use and under-estimate any effect of catheterisation.

5.3.8 **Exposure to institutionalised care**

Patients with a previous discharge destination 54 ‘NHS run care home’ or 85 ‘Non-NHS run care home’ were classified as having prior exposure to a care home. I was unable to match addresses to care homes as only non-identifiable postcode district (outward portion of the postcode) is available in IORD. Thus I will likely under-identify exposure to institutionalised care.

5.3.9 **Comorbidities and Charlson score**

Comorbidities, the hospital frailty score[297] and Charlson score[176,190] were calculated from diagnostic codes allocated to the admissions in which the positive blood culture was taken by previously reported methods. Standard practice in calculating the Charlson score is to use the dominant episode of the admission in question (the first episode in the admission, or if the main diagnosis code in this episode is a nonspecific 'R' code, using the second episode, unless this too is an R code)[177,189].

However, as discussed above, this has the potential both to under-record comorbidities, as UK coding guidance is to only code issues that are 'relevant to the admission', and over-record consequences of infection as co-morbidities. An alternative approach is to use only codes from prior admissions, to ensure that comorbidities were present prior to the bloodstream infection, rather than being sequelae. However it may also mean that patients who have no prior admissions in the dataset are wrongly identified as having no comorbidities. As such, both methods were used in this study, and considered in models.

5.3.10 **Procedures**

Operative and interventional procedures are recorded for all admissions by the clinical coding team using the NHS OPCS-4 Codes (Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures 4th Revision). These codes were classified into procedures by site according to previous NHS Digital guidance on surgical site infections[301].

5.3.11 **Statistical Methods**

All risk factors with frequency >1% in the analysis population were considered for association with resistant vs susceptible bloodstream infection in a univariate analysis, using ranksum tests for continuous variables and Fishers exact test for categorical variables. Variables were assessed for collinearity using Spearman correlation, and none were above

0.85. All variables were then entered in to a multivariable fractional polynomial model, with backward elimination at $p<0.10$ using alpha=0.05 to identify important non-linearity. All excluded variables were then re-added into the final identified model one at a time, and any variables which now had $p<0.05$ retained to create the final risk factor model.

Based on this risk factor model, the additional impact of antibiotic exposure was then assessed as any exposure in prior year, prior month, and days of therapy in the prior year[173] according to previous recommendations that antibiotic use be assessed using a range of metrics[302]. Antibiotic exposure was assessed as either oral, intravenous (IV) or both (intramuscular administration (rarely used) was grouped with IV administration on the basis it is not administered enterally); oral and IV routes were compared, and if there was no evidence of difference between these two estimates (using a Wald test for heterogeneity), a combined oral and IV exposure was included instead. The effects of each antibiotic exposure were assessed first in a univariate model, then added individually to the multivariate risk factor model. Risk factors from the original model were retained regardless of significance to adjust for confounding. Again any antibiotic exposures with $p<0.05$ were added one at a time to a final antibiotic and risk factor model and retained if $p<0.05$. Analysis was performed using Stata 15.1.

5.4 **RESULTS**

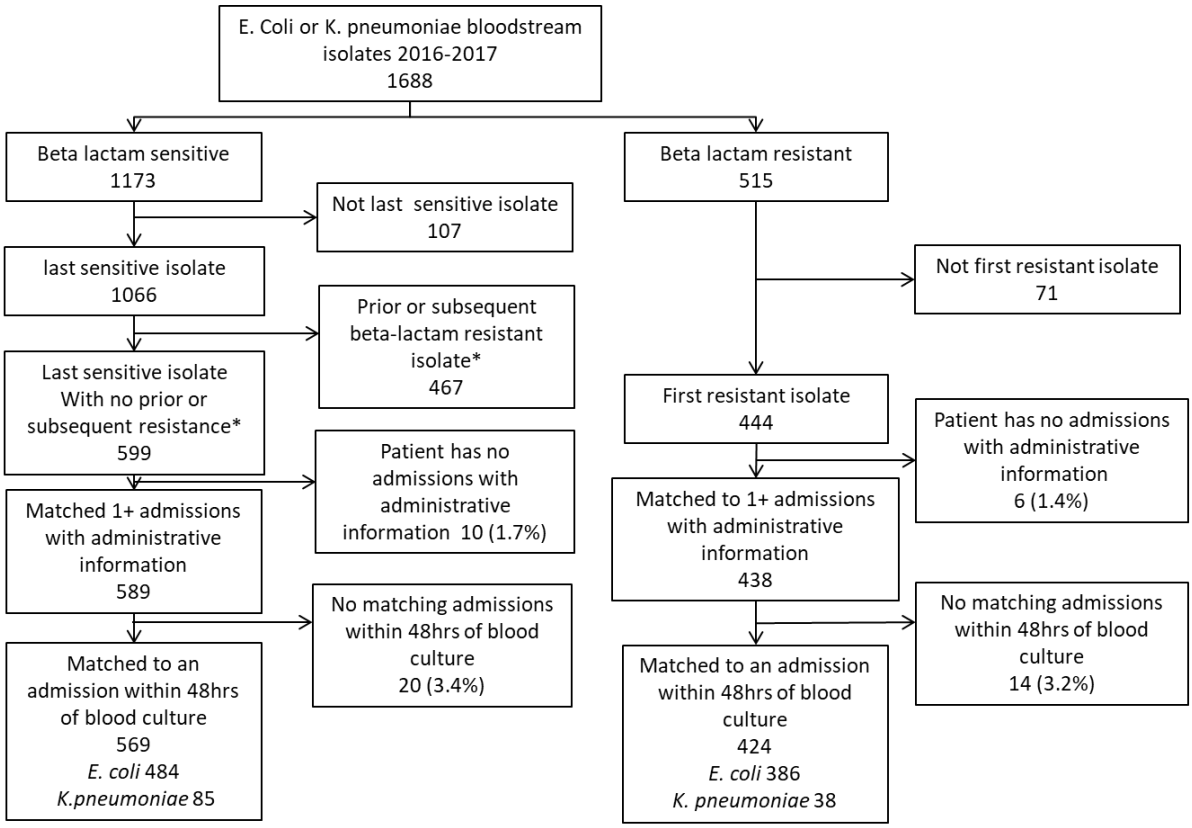
5.4.1 **Baseline characteristics and univariate analysis**

There were 993 individuals with a blood culture which grew *E. coli* (870) or *K. pneumoniae* (123) during 2016-2017 inclusive in Oxfordshire matched to an admission, of whom 569 only had susceptible isolates to beta-lactam antibiotics (last susceptible isolate taken as control) and 424 had one or more resistant isolates (first resistant isolate taken as a case) (**Figure 21**).

484/870(56%) *E. coli* isolates were susceptible to beta-lactams, and 85/123 (69%) *K. pneumoniae* isolates were susceptible. A small number of individuals were excluded due to lack of matching hospital administration data (total 50 (5%)), likely representing either errors in the underlying electronic data or failure to link across the different underlying electronic data sources, (**Table 28**).

Individuals with a resistant bloodstream infection were more likely to be male, had a catheter in the last year or month, had a previous admission, had an admission to haematology/oncology, ICU, medicine or surgery, admission or discharge to care home, were more likely to have current congestive cardiac failure or liver disease (in this admission) or previous liver disease (in the last year), and have had previous imaging, orthopaedic procedures, gastrointestinal procedures, and skin/soft tissue and procedures. They were more likely to have had a previous VRE or non-bloodstream beta-lactam resistant isolate in the past, the vast majority urinary (**Table 29**). They were also younger, had a higher Charlson score and hospital frailty score, more procedures, more blood draws, had visited more wards, and have more admissions, complex admissions and emergency admissions in the last year (**Table 30**). It is interesting to note that diabetes / diabetes complications was not identified as an independent risk factor for resistant infection, given that individuals with diabetes are more likely to get skin and soft tissue infections and antibiotics, and guidelines for treatment of diabetic foot infections or cellulitis in Oxfordshire involve the use of a broad-spectrum beta-lactam (co-amoxiclav), compared to a narrow spectrum beta-lactam (flucloxacillin) for individuals without diabetes.

It is worth noting that individuals with a resistant infection had spent longer in hospital prior to the bloodstream isolate being collected (Table 30). This analysis was conducted after the completion of the thesis after discussion with the examiners, and as such, this factor was not included in subsequent analysis.



*Any previous beta-lactam resistant *E.coli* or *K.pneumoniae* bloodstream isolate 1999 to time of collection or subsequently

Isolates with no matching admissions may represent samples from patients at community hospitals or from primary care services where the decision was made to manage the patient in the community, or the patient did not survive to hospital admission

Figure 21: Bloodstream isolates, matching to administrative information and selection for study

Table 27: Location details of non-matching isolates excluded from analysis if no admissions with administrative information (N=16)

Recorded location of blood collection	Susceptible	Resistant	Total
Community hospital	2	2	4
Emergency department	7	2	9
GP surgery	1	0	1
Ward	0	1	1
Other non-NHS hospital	0	1	1
Total	10	6	16

Table 28: Location details of non-matching isolates excluded from analysis if not matched to specific hospital admission (N=34??)

Recorded location of blood collection	Susceptible	Resistant	Total
Community hospital	9	4	13
Emergency Department*	7	8	15
GP surgery	3	0	3
Outpatient clinic	0	1	1
Other non-NHS hospital	1	1	2
Total	20	14	34

*confirmed no hospital spells that match the time frame despite Emergency Department blood culture taken, this may represent administrative error or linkage error.

Table 29: Baseline characteristics and univariate analysis of association with resistance – categorical variables (all in prior year unless otherwise stated)

	Beta-lactam susceptible N=569		Beta-lactam resistant N=424		All N=993		p (fishers exact)
	n	%	n	%	n	%	
Female	**304**	**53**	**193**	**46**	**497**	**50**	**0.008**
non-white ethnicity	22	4	19	4	41	4	0.372
Previous catheter (last year)	**76**	**13**	**77**	**18**	**153**	**15**	**0.024**
Previous catheter (last month)	**32**	**6**	**38**	**9**	**70**	**7**	**0.029**
Any prior admission	**316**	**56**	**289**	**68**	**605**	**61**	**<0.001**
Admission to haematology/oncology	**49**	**9**	**71**	**17**	**120**	**12**	**<0.001**
Admission to ICU	**41**	**7**	**50**	**12**	**91**	**9**	**0.009**
Admission to medicine	**234**	**41**	**207**	**49**	**441**	**44**	**0.009**
Admission to surgery	**203**	**36**	**192**	**45**	**395**	**40**	**0.001**
Admission or discharge to care home	**20**	**4**	**26**	**6**	**46**	**5**	**0.038**
Previous C. diff + isolate	8	1	8	2	16	2	0.363
Previous beta-lactam resistant isolate*	**22**	**4**	**86**	**20**	**108**	**11**	**<0.001**
Previous MRSA isolate	5	1	5	1	10	1	0.436
Previous VRE isolate	**4**	**1**	**10**	**2**	**14**	**1**	**0.028**
Acute myocardial infarction	35	6	28	7	63	6	0.435
Cerebrovascular disease	29	5	20	5	49	5	0.453
Congestive cardiac failure	**31**	**5**	**44**	**10**	**75**	**8**	**0.003**
Connective tissue disease	20	4	15	4	35	4	0.558
Dementia	58	10	47	11	105	11	0.363
Diabetes	126	22	94	22	220	22	0.526
Liver disease	**12**	**2**	**20**	**5**	**32**	**3**	**0.017**
Peptic ulcer disease	7	1	1	0	8	1	0.080
Peripheral vascular disease	30	5	28	7	58	6	0.227
Pulmonary disease	98	17	74	17	172	17	0.495
Cancer	123	22	110	26	233	23	0.065
Diabetic complications	8	1	7	2	15	2	0.475
Paraplegia	11	2	11	3	22	2	0.313
Renal disease	56	10	30	7	86	9	0.077
Metastatic cancer	44	8	39	9	83	8	0.238
Severe liver disease	11	2	12	3	23	2	0.236
HIV	0	0	2	0	2	0	0.182
Previous acute myocardial infarction	50	9	44	10	94	9	0.230
Previous cerebrovascular disease	40	7	29	7	69	7	0.506
Previous congestive cardiac failure	58	10	57	13	115	12	0.070
Previous connective tissue disease	28	5	20	5	48	5	0.503
Previous dementia	62	11	54	13	116	12	0.214
Previous diabetes	143	25	110	26	253	25	0.414
Previous liver disease	15	3	21	5	36	4	0.040
Previous peptic ulcer disease	11	2	6	1	17	2	0.358
Previous peripheral vascular disease	52	9	42	10	94	9	0.381
Previous pulmonary disease	123	22	104	25	227	23	0.158
Previous cancer	118	21	99	23	217	22	0.182
Previous diabetic complications	16	3	15	4	31	3	0.319
Previous paraplegia	18	3	17	4	35	4	0.293
Previous renal disease	83	15	59	14	142	14	0.419
Previous metastatic cancer	52	9	41	10	93	9	0.429
Previous severe liver disease	12	2	15	4	27	3	0.121
Previous HIV	0	0	2	0	2	0	0.182

	Beta-lactam susceptible N=569		Beta-lactam resistant N=424		All N=993		p (fishers exact)
	n	%	n	%	n	%	
Previous imaging procedure	**184**	**32**	**178**	**42**	**362**	**36**	**0.001**
Previous orthopaedic procedure	**62**	**11**	**70**	**17**	**132**	**13**	**0.007**
Pprevious gastrointestinal procedure	**102**	**18**	**112**	**26**	**214**	**22**	**0.001**
Previous genitourinary procedure	75	13	69	16	144	15	0.101
Previous vascular procedure	24	4	16	4	40	4	0.428
Previous skin/soft tissue procedure	**35**	**6**	**60**	**14**	**95**	**10**	**<0.001**
Previous endoscopy	64	11	59	14	123	12	0.122
Previous cardiothoracic procedure	30	5	32	8	62	6	0.092
Previous other surgery	68	12	54	13	122	12	0.390

* *E. coli* or *K. pneumoniae* isolate in non-bloodstream specimen (for breakdown).
Note: bold indicates univariate comparisons with p<0.05.

Table 30: Baseline characteristics and univariate analysis of association with resistance – continuous variables

	Beta-lactam susceptible N=569			Beta-lactam resistant N=424			All N=993			p (rank-sum)
	med	p25	p75	med	p25	p75	med	p25	p75	
Age	76	64	84	74	60	82	75	61	84	0.032
IMD score	10	6	15	10	6	16	10	6	16	0.481
Charlson score	**7**	**0**	**14**	**8**	**0**	**17**	**8**	**0**	**17**	**0.020**
Hospital frailty score	**1**	**0**	**4**	**2**	**0**	**5**	**1**	**0**	**5**	**<0.001**
Charlson score (previous admissions)	**1**	**0**	**3**	**2**	**1**	**4**	**2**	**0**	**4**	**<0.001**
Frailty score (concurrent admission)	**0**	**0**	**3**	**1**	**0**	**6**	**0**	**0**	**5**	**<0.001**
Number of previous procedures	5	2	9	6	3	9	6	3	9	0.159
Number of wards visited in previous year	**8**	**0**	**18**	**12**	**3**	**22**	**10**	**3**	**20**	**0.023**
Admissions in the previous year	**1**	**0**	**2**	**1**	**0**	**3**	**1**	**0**	**2**	**<0.001**
Complex admissions in previous year	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**1**	**<0.001**
Emergency admissions in previous year	**0**	**0**	**1**	**1**	**0**	**2**	**1**	**0**	**2**	**<0.001**
Hours as inpatient in hospital prior to blood culture collection*	**0.3**	**-2.4**	**7.2**	**0.8**	**-2.0**	**92.1**	**0.5**	**-2.2**	**21.2**	**<0.001**

Note: med=median, p25=lower limit of the IQR, p75=upper limit of the IQR. bold indicates univariate comparisons with p<0.05.

*patients in the emergency department are not counted as inpatients, thus patients with a blood culture taken in this setting will have a negative time as inpatient. This factor was investigated after discussion with examiners so is not considered in further models.

Table 31: Source of previous beta-lactam-resistant isolate prior to first resistant bloodstream isolate

Isolate type	Susceptible	Resistant	Total
Urine	22	75	97
Respiratory	0	4	4
Other*	0	7	7

*Other: abdominal swab, abdominal wound, gallbladder fluid, lumbar pus, pic line tip, suprapubic aspirate, tissue graft

5.4.2 Effect of calculating Charlson/frailty score using matched admission versus previous admissions

In an assessment of the effect of calculating Charlson score and frailty score based on a matched admission or data from prior admissions, it was evident that one issue with using prior admissions is that 388/993 (39%) of admissions in the study to which blood cultures were linked had no admission in the prior year. 253 (44%) of the 569 admissions with a susceptible isolate had no previous admission (in the prior year), compared with 135/424 (32%) of admissions with resistant isolates ($p<0.001$).

Calculating the Charlson Score based on prior admissions alone resulted in a lower median score (8, interquartile range (IQR) 0-17) compared to calculating Charlson score based on the current admission (10, IQR 3-20) (signrank $p<0.001$) which likely reflected the fact that over a third of the patients with an admission with a positive *E.coli/K. pneumoniae* blood culture had no admissions in the prior year. The Spearman rank correlation coefficient was 0.85, and Lin's concordance coefficient was 0.32. However, the impact of calculating the frailty score based on prior admissions (as originally designed) was much greater, with a median 0 (IQR

0-4.7) compared to a median of 5.5 calculated on the matched admission (IQR 2.7-8.7) (signrank p<0.001). The Spearman rank correlation coefficient was 0.25, and Lin's concordance coefficient 0.23. I offered Charlson score and frailty score calculated both ways to the model.

The potential advantage of using prior admissions to calculate comorbid status (rather than discharge codes of the linked admission) is that this can potentially capture more past medical issues, and avoids the issue of recording the sequelae, rather than pre-existing risk-factors for an infection. However it is apparent that doing so, at least in the context of bloodstream infections and 1 year of prior data, may lead to significant loss of information.

5.4.3 Building the multivariate model based on exposures associated with resistant bloodstream infections

In a multivariate analysis, using all the risk factors associated with resistance in a univariate analysis (**Table 29** and **Table 30**) and applying backwards elimination with exit p=0.1, resistant bloodstream infections were independently more common in those with: more emergency admissions, any skin/soft tissue procedure, or any admission to haematology/oncology in the prior year; congestive cardiac failure (present in the dominant episode of the admission with the best match in time to the blood culture – see methods) and men. Having a previous non-blood culture specimen with a beta-lactam-resistant *E.coli* or *K. pneumoniae* was also strongly associated with risk of resistant bloodstream infection (Odds Ratio (OR)=5.63 95% CI 3.41-9.33) (**Table 32**).

It was interesting to note that none of the scores measuring comorbidity were associated with resistant infection in this model – neither Charlson nor the frailty score, calculated using matched or prior admissions, were present in the final model.

Table 32: Multivariate analysis model, risk factors only (no antibiotics)

	OR	p	95% CI	
Previous beta-lactam-resistant non-blood isolate	5.63	<0.001	3.41	9.33
Number of emergency admissions in the last year (per 1 higher)	1.18	0.001	1.07	1.29
Any admission to a haematology/oncology ward in prior year	1.79	0.008	1.17	2.74
Congestive cardiac failure in admission matched to culture	2.00	0.007	1.21	3.32
Skin/soft tissue procedure in the prior year	1.82	0.013	1.14	2.92
Female vs male	0.72	0.016	0.55	0.94

5.4.4 **Antibiotic exposure: individual antibiotic exposure models**

The only antibiotic classes that differed in effect on resistant vs susceptible bloodstream infection depending on route of administration (oral or IV) in univariate analyses were access list beta-lactams and non-gram-negative-active beta-lactams, and all antibiotics grouped together. As previously discussed, these first two antibiotic groups are highly similar, with the only difference being that amoxicillin is classified as an 'access' list beta-lactam, but is a gram-negative-active beta-lactam. As such these were analysed separately, and all other classes analysed by class only (

Table 33). It is worth noting that when overall number of exposures were small, then no difference in effect found may be due to lack of power to detect the effect, rather than true absence of difference between intravenous and oral preparations. Also for antibiotics where there is no available intravenous preparation (such as with trimethoprim, tetracyclines or nitrofurantoin) then comparison is not possible.

Table 33: Wald tests for heterogeneity of effect between oral and IV routes according to antibiotic group/class and exposure in the prior year and month (bivariate models)

Class	Exposure in prior year p	Exposure in prior month p
All drugs	**0.00**	**0.01**
All beta-lactams	0.74	0.84
Access list beta-lactam	**0.01**	**0.02**
Watch list beta-lactam	0.53	0.21
Non-gram-negative-active beta-Lactam	**<0.001**	**0.03**
Gram-negative-active beta-lactam	0.26	0.29
Aminoglycosides	0.06	0.42
Anti-anaerobe	0.91	0.73
Clindamycin	0.54	0.71
Macrolide	0.25	0.12
Nitrofurantoin*	-	-
Quinolone	0.60	0.97
Tetracycline**	-	-
Vancomycin	0.41	0.60
Other	0.08	0.95
Anti-folate	0.38	0.83
Trimethoprim***	-	-
Co-trimoxazole	0.41	0.88

**no IV nitrofurantoin used
*** no IV tetracycline used
*** no IV trimethoprim used
Note: bivariate model containing each exposure as IV and oral, and testing whether the effect of IV exposure on risk of a beta-lactam resistant bloodstream infection is the same as the effect of oral exposure.

5.4.5 **Analysis of antibiotic exposure in prior month**

5.4.5.1 ***Antibiotics associated with beta-lactam resistance in univariate and multivariate analysis***

In a univariate analysis of antibiotic exposure in the prior month, not adjusting for clinical risk factors, exposure to antibiotics, both IV and oral, and exposure to multiple classes of antibiotic were associated with beta-lactam resistant infections, with only access list/non-

gram-negative-active beta-lactams IV, clindamycin, tetracycline and vancomycin not being associated with beta-lactam resistance (**Table 34**).

Analysing exposure whilst adjusting for clinical risk factors previously identified as being associated with beta-lactam resistance (**Table 32**), antibiotic groupings associated with beta-lactam resistant bloodstream infections were any antibiotic exposure (OR=1.76 95% CI 1.23-2.53 p=0.002), oral antibiotic exposure (but not intravenous exposure) (OR=2.08 95% CI 1.29-3.34 p=0.002), any beta-lactam exposure (OR=1.50 95% CI 1.07-2.10 p=0.019), watch-list beta-lactams exposure (OR=1.42 95% CI 1.00-2.00 p=0.049), gram-negative-active beta-lactams exposure (OR=1.45 95% CI 1.03-2.05 p=0.034), access list beta-lactams given orally (OR=2.19 95% CI 1.06-4.48 p=0.035), non-gram-negative-active beta-lactams given orally (OR=2.46 95% CI 1.02-5.96 p=0.045), gram negative beta-lactams (OR =1.45 95% CI 1.03-2.05 p=0.034) and anti-folate antibiotics (OR=2.51 95% CI 1.07-5.91 p=0.035) (**Table 34**).

5.4.5.2 *Antibiotic exposure: multiple antibiotic exposure models*

The final model of antibiotic exposure in the prior month was run with gram-negative-active beta-lactam exposure, oral non-gram-negative-active beta-lactam exposure, and anti-folate antibiotic exposure together with the previously-associated clinical factors of previous beta-lactam-resistant isolate, congestive cardiac failure, female sex, number of emergency admissions in the prior year, admission to a haematology/oncology ward and skin/soft tissue infection (**Table 35**). In this there was no evidence of any antibiotics being independently significantly associated with resistant bloodstream infections. Including these multiple antibiotics in the same model resulted in a reduction in the association between resistance and exposure to the individual antibiotic classes. This may be because there was a high degree of overlap between patients exposed to the antibiotic classes, i.e. due to confounding. Prior skin/soft tissue procedure also had a reduction in association with evidence for association correspondingly weakening (p=0.074, 95% CI 0.96-2.57) – this again may reflect

confounding with concurrent antibiotic exposures, and once this was accounted for, the association was reduced.

5.4.5.3 *Quantitative analysis of antimicrobial use and risk of beta-lactam resistance*

In analyses including any antibiotic exposure and quantitative measurements of days of therapy (truncating at 95th percentile to reduce the impact of outliers), I did not find evidence of an association with increasing number of days of 'watch list' beta-lactams (for every additional 7 days OR=0.99 95% CI 0.84-1.16 p=0.86) (**Table 36**) although power was low to exclude modest effects given the relatively short exposures (median 5 days in the last year, IQR 2-9 days). Indeed there was no evidence of an independent effect of additional days of exposure in the prior month and beta-lactam resistant bloodstream infection for any antibiotic/group (**Table 36**), having accounted for the effects of any exposure at all.

For all antibiotics/groups, the best selected model was linear, that is every additional day of antibiotics was associated with the same impact on the risk (on the log-odds scale) of resistant vs susceptible infection.

One hypothesis I had as to why no significant association was seen between antibiotic duration and resistance was that the actual relationship may be non-linear, and due to the relatively modest dataset size (~1000 individuals) the algorithm to chose the best model was selecting a linear relationship because of limited power. As a way of testing this, I replicated the data four times (to increase power) and re-ran the analysis; however, the algorithm still selected a linear relationship. This neither confirms nor refutes that other models may be better fits of the data, and ultimately more data will be required to explore this question further

Table 34: Antibiotic exposure in prior month and association with beta-lactam resistance: univariate and multivariate analysis

Antibiotic exposure in the prior year by class	Beta-lactam susceptible (N=569)		Beta-lactam resistant (N=424)		All (N=993)		p	Multivariate analysis*			
	n	%	n	%	n	%	univariate	OR	95% CI		p
Any antibiotic	**74**	**13**	**117**	**28**	**191**	**19**	**0.000**	**1.76**	**1.23**	**2.53**	**0.002**
Any antibiotic IV	56	10	65	15	121	12	0.006	1.26	0.83	1.92	0.276
Any antibiotic orally	**34**	**6**	**75**	**18**	**109**	**11**	**0.000**	**2.08**	**1.29**	**3.34**	**0.002**
Beta-lactams	**105**	**18**	**136**	**32**	**241**	**24**	**0.000**	**1.50**	**1.07**	**2.10**	**0.019**
Access list beta-lactam IV	14	2	10	2	24	2	0.546	0.77	0.32	1.86	0.558
Access list beta-lactam orally	**13**	**2**	**28**	**7**	**41**	**4**	**0.001**	**2.18**	**1.06**	**4.48**	**0.035**
Watch list beta-lactam	**97**	**17**	**122**	**29**	**219**	**22**	**0.000**	**1.42**	**1.00**	**2.00**	**0.049**
Nongramneg beta-lactam IV	11	2	8	2	19	2	0.576	0.73	0.27	1.96	0.528
Nongramneg beta-lactam orally	**8**	**1**	**20**	**5**	**28**	**3**	**0.002**	**2.46**	**1.02**	**5.96**	**0.045**
Gram-negative active beta-lactam	**97**	**17**	**124**	**29**	**221**	**22**	**0.000**	**1.45**	**1.03**	**2.05**	**0.034**
Aminoglycoside	39	7	44	10	83	8	0.031	1.18	0.72	1.93	0.507
Anti-anaerobe	40	7	48	11	88	9	0.013	1.41	0.88	2.26	0.152
Clindamycin	3	1	2	0	5	1	0.635	0.71	0.10	5.15	0.734
Macrolide	7	1	13	3	20	2	0.036	1.13	0.41	3.14	0.811
Nitrofurantoin	2	0	9	2	11	1	0.010	3.41	0.65	17.97	0.148
Quinolone	1	0	9	2	10	1	0.003	5.99	0.70	50.99	0.102
Tetracycline	3	1	2	0	5	1	0.635	0.61	0.08	4.50	0.629
Vancomycin	11	2	9	2	20	2	0.503	0.58	0.22	1.55	0.278
Other	2	0	12	3	14	1	0.001	4.76	0.99	22.99	0.052
Anti-folate	**8**	**1**	**24**	**6**	**32**	**3**	**0.000**	**2.51**	**1.07**	**5.91**	**0.035**
Trimethoprim	3	1	10	2	13	1	0.013	2.82	0.70	11.30	0.144
Co-trimoxazole	5	1	14	3	19	2	0.006	2.31	0.78	6.80	0.129

* multivariate analysis including each antibiotic exposure shown alone but adjusted for risk factors in the multivariate analysis (Table 32) congestive cardiac failure documented during matched admission to bloodstream isolate, at least one admission in prior year to a haematology/oncology ward, skin/soft tissue procedure in the prior year, previous beta-lactam-resistant isolate, female sex, and number of emergency admissions.

Note: p25, p50, p75 indicate the lower limit of the IQR, the median, and the upper limit of the IQR in those with any exposure.

Table 35: Multivariate model of antibiotic use in the prior month and risk of resistant infection

	Odds Ratio	p	95% CI	
Gram-negative active beta-lactam in prior month (oral or IV)	1.34	0.094	0.95	1.91
Non gram negative active beta-lactam orally in prior month	2.34	0.059	0.97	5.68
Antifolate antibiotic in prior month	2.54	0.190	0.63	10.3
Previous beta-lactam-resistant non-blood isolate	5.64	<0.001	3.40	9.35
Number of emergency admissions in prior year (per one extra admission)	1.15	0.004	1.05	1.27
At least one admission to a Haematology/Oncology Ward	1.68	0.019	1.09	2.59
Congestive cardiac failure in admission matched to culture	1.93	0.011	1.16	3.22
Skin/soft tissue procedure	1.57	0.074	0.96	2.57
Female sex v male	0.73	0.022	0.56	0.96

Table 36: Antibiotic exposure: days of therapy in prior month and association with resistance in univariate and multivariate model

	Beta-lactam susceptible (N=569)				Beta-lactam resistant (N=424)				All (N =993)					Multivariate analysis (per 1 day of therapy)			
	any exposure	p25	p50	p75	any exposure	p25	p50	p75	any exposure	p25	p50	p75	p ranksum	OR	95% CI		p
Any antibiotic	74	1	2	6	117	3	1	7	191	2	1	6	<0.001	1.01	0.94	1.09	0.785
Any antibiotic IV	56	1	1	3	65	1	1	3	121	1	1	3	0.009	0.99	0.86	1.13	0.855
Any antibiotic orally	34	1	4	6	75	3	2	7	109	3	2	7	<0.001	1.00	0.89	1.11	0.979
Beta-lactams	105	2	5	8	136	6	3	10	241	6	2	9	<0.001	1.01	0.96	1.06	0.624
Access list beta-lactam IV	14	1	2	3	10	1	1	2	24	1	1	3	0.911	0.73	0.37	1.46	0.376
Access list beta-lactam orally	13	2	3	4	28	4	2	9	41	4	2	7	0.001	1.07	0.91	1.26	0.413
Watch list beta-lactam	97	2	5	8	122	5	3	9	219	5	2	9	<0.001	1.01	0.96	1.06	0.776
Nongramneg beta-lactam IV	11	1	1	3	8	1	1	3	19	1	1	3	0.957	0.83	0.51	1.37	0.474
Nongramneg betalactam oral	8	2	3	6	20	4	2	10	28	3	2	8	0.002	1.05	0.90	1.24	0.521
Gramneg active beta-lactam	97	2	5	8	124	6	3	10	221	5	2	9	<0.001	1.01	0.95	1.06	0.856
Aminoglycoside	39	1	1	2	44	1	1	2	83	1	1	2	0.049	0.88	0.31	2.47	0.810
Anti-anaerobe	40	1	2	6	48	3	2	7	88	3	1	6	0.016	0.98	0.87	1.10	0.698
Clindamycin	3	1	3	3	2	11	8	14	5	3	3	8	0.907	-	0.00	-	0.981
Cephalosporin	12	2	4	9	13	4	2	5	25	4	2	5	0.341	0.90	0.69	1.16	0.404
Macrolide	7	1	2	3	13	5	2	6	20	4	1	6	0.040	1.32	0.88	2.00	0.184
Nitrofurantoin	2	2	3	4	9	4	1	4	11	4	1	4	0.008	1.17	0.40	3.44	0.769
Quinolone	1	6	6	6	9	4	2	7	10	5	2	7	0.002	0.79	0.36	1.72	0.551
Tetracycline	3	2	3	3	2	2	1	3	5	3	2	3	0.901	0.22	0.02	2.99	0.258
Vancomycin	11	1	2	12	9	3	2	12	20	3	1	12	0.824	1.04	0.89	1.20	0.638
Other	2	4	7	10	12	3	1	14	14	4	1	14	0.001	0.95	0.77	1.16	0.592
Anti-folate	8	3	4	5	24	3	2	5	32	3	2	5	<0.001	0.99	0.74	1.32	0.939
Trimethoprim	3	3	4	4	10	2	1	3	13	2	1	4	0.012	0.62	0.23	1.65	0.335
Co-trimoxazole	5	2	4	5	14	4	3	5	19	4	2	5	0.006	1.06	0.77	1.46	0.727

* multivariate analysis including each antibiotic exposure shown alone but adjusted for risk factors: any exposure to an antibiotic in prior month (multivariate analysis estimates effect of subsequent extra days of therapy) congestive cardiac failure documented during matched admission to bloodstream isolate, at least one admission in prior year to a haematology/oncology ward, skin/soft tissue procedure in the prior year, previous beta-lactam-resistant isolate, female sex, and number of emergency admissions. All variables were to power 1.

Note: p25, p50, p75 indicate the lower limit of the IQR, the median, and the upper limit of the IQR in those with any exposure.

5.4.6 Analysis of antibiotic exposure in prior year, and differences with prior month analysis

5.4.6.1 *Antibiotics associated with beta-lactam resistance in univariate and multivariate analysis*

I repeated the analyses detailed above for exposure in the prior year, rather than prior month. In a univariate analysis of antibiotic exposure in the prior year not adjusting for clinical risk factors, exposure to antibiotics, both IV and oral, and exposure to multiple classes of antibiotic were associated with beta-lactam resistant infections, similar to the prior month analysis. The only classes that were not associated with resistance univariately were access list/non-gram-negative active beta-lactams intravenously, and clindamycin and tetracyclinesTable 37. Unlike the prior month analysis, there was no evidence of significant association between vancomycin and beta-lactam resistance.

When other risk factors were controlled for , but considering each antibiotic/class one at a time, only watch list beta-lactams and gram-negative beta-lactams exposure in the prior year remained associated with beta-lactam resistant bloodstream infections (OR=1.46 95% CI 1.04-2.04 p=0.027 and OR=1.45 95% CI 1.04-2.03 p=0.027 respectively) (**Table 37**). Unlike the prior month analysis, there was no evidence of significant association seen with any antibiotic exposure, oral antibiotic exposure, any beta-lactam exposure, access-list beta-lactams given orally, non-gram-negative beta lactams given orally, or anti-folate antibiotics.

5.4.6.2 *Antibiotic exposure: multiple antibiotic exposure models*

There was high collinearity (Spearman rank correlation coefficient 0.98) between the two antibiotic factors associated with beta-lactam resistance in the multivariate model (‘watch list’ beta-lactams and gram-negative beta-lactams exposure), which is unsurprising given that they are highly similar groups, differing only in the inclusion of amoxicillin as a gram-negative beta-lactam, but not a ‘watch list’ beta-lactam). . The final model for gram-negative-

active beta-lactams and 'watch list' classification beta-lactams is shown in **Table 38A and 38B** with both performing very similarly.

5.4.6.3 *Quantitative analysis of antimicrobial use and risk of beta-lactam resistance*

In analyses including any antibiotic exposure and quantitative measurements of days of therapy (truncating at 95th percentile to reduce the impact of outliers), similarly to the results for prior month analysis, I did not find any evidence of an independent effect of additional days of exposure in the prior month and beta-lactam resistant bloodstream infection for any antibiotic/group (**Table 39**), having accounted for the effects of any exposure at all.

Table 37 Antibiotic exposure in prior year and association with beta-lactam resistance: univariate and multivariate analysis

Antibiotic exposure in the prior year by class	Beta-lactam susceptible (N=569)		Beta-lactam resistant (N=424)		All (N=993)		p	Multivariate analysis*			
	n	%	n	%	n	%	univariate	OR	95% CI		p
Any antibiotic	185	33	206	49	391	39	<0.001	1.14	0.82	1.59	0.446
Any antibiotic IV	149	26	146	34	295	30	0.003	0.88	0.63	1.23	0.441
Any antibiotic orally	108	19	153	36	261	26	<0.001	1.39	0.96	2.02	0.084
Beta-lactams	211	37	235	55	446	45	<0.001	1.35	0.97	1.88	0.080
Access list beta-lactam IV	45	8	33	8	78	8	0.520	0.62	0.36	1.05	0.075
Access list beta-lactam orally	37	7	54	13	91	9	0.001	1.34	0.82	2.22	0.247
Watch list beta-lactam	**189**	**33**	**222**	**52**	**411**	**41**	**<0.001**	**1.46**	**1.04**	**2.04**	**0.027**
Nongramneg beta-lactam IV	32	6	23	5	55	6	0.504	0.57	0.30	1.06	0.074
Nongramneg beta-lactam orally	14	2	30	7	44	4	<0.001	1.86	0.92	3.77	0.086
Gram-negative active beta-lactam	**194**	**34**	**226**	**53**	**420**	**42**	**<0.001**	**1.45**	**1.04**	**2.03**	**0.027**
Aminoglycoside	120	21	112	26	232	23	0.030	0.78	0.55	1.11	0.165
Anti-anaerobe	84	15	100	24	184	19	<0.001	1.19	0.82	1.73	0.348
Clindamycin	8	1	9	2	17	2	0.268	0.72	0.24	2.17	0.565
Macrolide	45	8	48	11	93	9	0.044	0.83	0.50	1.37	0.462
Nitrofurantoin	21	4	30	7	51	5	0.013	1.10	0.57	2.10	0.778
Quinolone	23	4	32	8	55	6	0.013	0.85	0.44	1.64	0.631
Tetracycline	5	1	9	2	14	1	0.086	1.41	0.42	4.75	0.580
Vancomycin	27	5	27	6	54	5	0.165	0.62	0.32	1.16	0.136
Other	13	2	23	5	36	4	0.007	1.21	0.56	2.64	0.628
Anti-folate	21	4	44	10	65	7	<0.001	1.71	0.95	3.10	0.075
Trimethoprim	10	2	22	5	32	3	0.002	1.95	0.83	4.56	0.123
Co-trimoxazole	11	2	22	5	33	3	0.004	1.47	0.66	3.29	0.344

* multivariate analysis including each antibiotic exposure shown alone but adjusted for risk factors in the multivariate analysis (Table 32), specifically: congestive cardiac failure documented during matched admission to bloodstream isolate, at least one admission in prior year to a haematology/oncology ward, skin/soft tissue procedure in the prior year, previous beta-lactam-resistant isolate, female sex, and number of emergency admissions. Bold indicates antibiotic factors with p<0.05 when adjusted for these clinical risk factors

Table 38: Multivariate model of antibiotic use in the prior year and risk of resistant infection

	Odds Ratio	p	95% CI	
Table 38A Broad spectrum beta-lactam model based on gram-negative activity (amoxicillin included)				
Gram-negative active beta-lactam in prior year (oral or IV)	1.45	0.027	1.04	2.03
Previous beta-lactam-resistant non-blood isolate	5.76	<0.001	3.47	9.55
Number of emergency admissions in the last year (per 1 higher)	1.10	0.069	0.88	1.23
At least one admission to a Haematology/Oncology ward in prior year	1.69	0.016	1.10	2.60
Congestive cardiac failure in admission matched to culture	2.00	0.007	1.21	3.32
Skin/soft tissue procedure in the prior year	1.60	0.056	0.99	2.60
Female sex v male	0.74	0.026	0.56	0.96
Table 38B Broad spectrum beta-lactam model based on UK 'Watch' list classification (amoxicillin not included)				
'Watch' list beta-lactam in prior year (oral or IV)	1.46	0.027	1.04	2.04
Previous beta-lactam-resistant non-blood isolate	5.76	<0.001	3.47	9.55
Number of emergency admissions in the last year (per 1 higher)	1.11	0.067	0.88	1.23
At least one admission to a Haematology/Oncology ward in prior year	1.69	0.017	1.10	2.60
Congestive cardiac failure in admission matched to culture	2.03	0.006	1.22	3.34
Skin/soft tissue procedure in the prior year	1.60	0.059	0.98	2.59
Female sex v male	0.74	0.029	0.56	0.97

Table 39: Antibiotic exposure: days of therapy in prior year and association with resistance in univariate and multivariate analysis

	Beta-lactam susceptible (N=569)				Beta-lactam resistant (N=424)				All (N =993)					Multivariate analysis (per 7 days of therapy)			
	any exposure	p25	p50	p75	any exposure	p25	p50	p75	any exposure	p25	p50	p75	p ranksum	OR	95% CI		p
Any antibiotic	74	1	2	6	117	3	1	7	191	2	1	6	0.000	1.01	0.86	1.19	0.906
Any antibiotic IV	56	1	1	3	65	1	1	3	121	1	1	3	0.009	1.01	0.68	1.50	0.954
Any antibiotic orally	34	1	4	6	75	3	2	7	109	3	2	7	0.000	1.00	0.81	1.25	0.964
Beta-lactams	105	2	5	8	136	6	3	10	241	6	2	9	0.000	1.03	0.89	1.18	0.734
Access list β-lactam IV	14	1	2	3	10	1	1	2	24	1	1	3	0.911	0.46	0.15	1.40	0.172
Access list β-lactam orally	13	2	3	4	28	4	2	9	41	4	2	7	0.001	1.22	0.61	2.43	0.573
Watch list β-lactam	97	2	5	8	122	5	3	9	219	5	2	9	0.000	0.99	0.84	1.16	0.858
Nongramneg β-lactam IV	11	1	1	3	8	1	1	3	19	1	1	3	0.957	0.51	0.19	1.32	0.165
Nongramneg β-lactam oral	8	2	3	6	20	4	2	10	28	3	2	8	0.002	1.06	0.56	2.00	0.860
Gramneg active β-lactam	97	2	5	8	124	6	3	10	221	5	2	9	0.000	0.98	0.84	1.15	0.845
Aminoglycoside	39	1	1	2	44	1	1	2	83	1	1	2	0.049	1.10	0.17	7.10	0.921
Anti-anaerobe	40	1	2	6	48	3	2	7	88	3	1	6	0.016	0.94	0.70	1.26	0.687
Clindamycin	3	1	3	3	2	11	8	14	5	3	3	8	0.907	1.01	0.30	3.40	0.984
Cephalosporin	12	2	4	9	13	4	2	5	25	4	2	5	0.341	0.88	0.48	1.61	0.670
Macrolide	7	1	2	3	13	5	2	6	20	4	1	6	0.040	1.58	0.60	4.16	0.355
Nitrofurantoin	2	2	3	4	9	4	1	4	11	4	1	4	0.008	1.60	0.42	6.10	0.490
Quinolone	1	6	6	6	9	4	2	7	10	5	2	7	0.002	1.18	0.55	2.54	0.679

*multivariate analysis including each antibiotic exposure shown alone but adjusted for risk factors: any exposure to the antibiotic shown in prior year (multivariate analysis above estimates effect of subsequent extra days of therapy), congestive cardiac failure documented during matched admission to bloodstream isolate, at least one admission in prior year to a haematology/oncology ward, skin/soft tissue procedure in the prior year, previous beta-lactam-resistant isolate, female sex, and number of emergency admissions. All variables were selected with power 1, ie linear relationship between exposure and outcome on the log-odds scale.
Note: p25, p50, p75 indicate the lower limit of the IQR, the median, and the upper limit of the IQR in those with any exposure.

5.4.7 Using 'Access/Watch' list classification of beta-lactams versus gram-negative activity of beta-lactams

Similar results were obtained when using the 'UK Access/Watch list' classification of a broad-spectrum beta-lactams compared to using gram-negative activity to define broad-spectrum beta-lactams. In particular, after adjusting for clinical factors, there was a significant association between broad-spectrum beta-lactam exposure **in the prior month** and resistance whether or not amoxicillin was included as a broad-spectrum beta-lactam**.** This may be chiefly because the number of patients with positive blood cultures exposed to amoxicillin who had not already been exposed to another broad-spectrum beta-lactam was small - only two additional patients with a positive blood culture had been exposed to amoxicillin but not any other broad-spectrum beta-lactam (increasing numbers exposed from 219 ('watch list' classification) to 221 (gram-negative active classification) leading to very similar associations between beta-lactam resistant bloodstream infections and exposure to watch-list beta-lactams (OR=1.42 95% CI 1.00-2.00 p=0.049) and gram-negative-active beta-lactams (OR=1.45 95% CI 1.03-2.05 p=0.034) as in **Table 34**.

In terms of antibiotic exposure **in the prior year** and resistance, results again were similar whether or not amoxicillin was included as a broad-spectrum beta-lactam (OR=1.45 95% CI 1.04-2.03 p=0.027 and OR=1.46 95% CI 1.04-2.04 p=0.027 respectively. 9 patients in total were exposed to amoxicillin but not other broad-spectrum beta-lactams, increasing numbers exposed from 411 ('watch list') to 420 ('gram-negative active')cases and controls) (**Table 37).**

5.5 DISCUSSION

5.5.1 Association of antibiotic classes/groups and resistance

In a multivariate analysis of 993 patients with an *E. coli* or *K. pneumoniae* bloodstream infection, any hospital antibiotics, any oral hospital antibiotics, beta-lactam antibiotics, gram-negative-active beta-lactams, non-gram-negative-active beta-lactams orally (but not IV) and anti-folate antibiotics in the prior month were associated with having a beta-lactam resistant infection rather than a beta-lactam susceptible infection. In a prior year analysis, exposure to hospital gram-negative-active beta-lactams and broad-spectrum beta-lactams on the UK 'Watch' list in the prior year was associated with higher risk of the isolate being resistant to beta-lactam antibiotics

5.5.2 Broad-spectrum versus narrow-spectrum beta-lactam antibiotics, and year compared to month effects

In terms of exposure in the prior month, broad-spectrum beta-lactam exposure (either defined as 'on the UK 'Watch' List as "should be prescribed only for specific indications, since they are at higher risk of bacterial resistance", or based on gram-negative activity) was associated with beta-lactam resistant infections. I found an association between narrow-spectrum beta-lactams given orally and beta-lactam resistant infections, but no evidence of association when given intravenously. However, for the intravenous comparison, the upper 95% CI limit shows that my data is compatible with up to a two-fold increase in risk (OR 0.73, 95% CI 0.27-1.96 p=0.528) .

An analysis of exposure in the prior year, there was again an association between broad-spectrum beta-lactam exposure, based on both 'Watch list' and gram-negative activity definitions). However unlike the prior month analysis I did not identify a significant association between exposure to narrow-spectrum beta-lactams on the UK 'Access' list ("first

and second choice for common infections") or non-gram-negative-active beta-lactams. For IV administrations of these two classes, the upper 95% CI for the odds ratios were much lower (OR 0.62, 95% CI 0.36-1.05 p=0.075 and OR 0.57, 95% CI 0.30-1.06 p=0.074 respectively). This means I can exclude important positive associations with these classes. However, for oral administrations, the upper 95% CI were 2.22 and 3.77 respectively (OR 1.34, 95% CI 0.82–2.22, p=0.247 and OR 1.86, 95% CI 0.92-3.77, p=0.086), meaning that my data are still compatible with large associations with these classes, i.e. up to doubling or even quadrupling of risk, and therefore that lack of significance may reflect lack of power (due to limitations of study size) rather than lack of genuine effect. (Very similar numbers are seen when defining narrow-spectrum beta-lactams based on lack of gram-negative activity.)

However one would normally expect analyses with more exposure data to have greater power to detect associations. Despite having more exposures to antibiotics in a prior year vs prior month analysis, fewer associations were found. It is possible that the time since last exposure may have some effect on risk of resistant infection; had I modelled this, I may have been able to show an association.

Additionally there may be different time-dependent effects depending on spectrum of antibiotics. For instance, one hypothesis may be that broad-spectrum beta-lactams are more likely to have long-standing effects due to widespread ecological disturbance causing long-term changes in the composition of the host microflora and increased long-term colonisation with resistant strains, meaning patients are at increased risk of subsequent invasive infection from these strains over much longer time periods. Conversely, exposure to narrow-spectrum beta-lactams may cause a lesser and more transient disruption, such that after a month or two with slightly increased prevalence of resistant strains, the host microflora has more-successfully returned to pre-antibiotic state, and the likelihood of ongoing presence of

resistance strains is much less compared to the larger disruption of the broad-spectrum antibiotics.

Taken together, these findings do support the suggestion that broad-spectrum beta-lactam exposure may increase the risk of subsequent beta-lactam resistant infection more than narrow-spectrum exposure, but there may still be effects of narrow-spectrum antibiotics, particularly when taken orally, though they may be more transient.

5.5.3 **Oral vs intravenous comparison**

Exposure to an oral hospital antibiotic in the prior month was associated with an increased risk of beta-lactam resistant bloodstream infection, whilst there was no association found between IV antibiotic exposure and resistance. This is the first analysis I am aware of that specifically studies mode of delivery (oral vs IV), and clearly requires replication in other studies. One hypothesis would be that the gut bacteria are exposed to higher levels of antibiotic if the drug is delivered orally, and therefore more likely to disrupt the gut microbiota, lead to overabundance of resistant strains, and subsequent infection with these strains, a phenomenon which has been observed previously in mouse models[128].

The only specific drug class that differed in association with beta-lactam resistant bloodstream infection depending on route of delivery was the narrow-spectrum beta-lactams (defined either by presence on the UK 'Access' list or lack of gram-negative activity). The antibiotics which form this group – penicillin, flucloxacillin, and amoxicillin in the 'access list' – are primarily renally excreted, with around 60% of the drug recoverable from urine. However, around 4% is excreted from the biliary tree[303,304], which provides biological plausibility to the hypothesis that administration of these antibiotics intravenously may result

in little selective pressure in the gut, if this is a key site of resistance selection for Enterobacteriaceae.

The broad-spectrum beta-lactams include ceftriaxone, piperacillin/tazobactam and carbapenems, antibiotics which, although administered intravenously, have high levels of biliary excretion or penetration[156,305,306]. This may be another possible reason why there was no significant difference found between oral and IV routes of administration of these broad-spectrum beta-lactams in terms of their association with resistance.

It is also possible that formulary may affect the comparison of oral vs IV effects. For instance ciprofloxacin, previously linked to beta-lactam resistance, is almost always given orally in my dataset, thus the fact I found no evidence of differences in effect between oral and IV administration likely reflects the composition of my data rather than any biological effects.

5.5.4 Associations between non-beta-lactam antibiotic exposure and beta-lactam resistance

One explanation for the association between (hospital) trimethoprim exposure in the prior month and beta-lactam resistant bloodstream infection is that it is a marker of a patient with significant urinary symptoms and multiple previous courses of antibiotics. A similar effect was postulated by Sogaard et al[307] in their study of community antibiotic use and ESBL Enterobacteriaceae urinary tract infections, where they found an association between community nitrofurantoin use and beta-lactam resistant infections.

Another possible explanation is that trimethoprim use may be selecting for beta-lactam resistance due to cross resistance. Previous work has suggested that trimethoprim and amoxicillin co-selection can occur[308]. Pouwels et al[52] analysed trimethoprim resistance in over two million Enterobacteriaceae-positive urine samples in England 2014-2016, and

compared geographical patterns of resistance with antibiotic prescribing. They found that amoxicillin/ampicillin use explained more of the variance of trimethoprim resistance than trimethoprim use, suggesting that co-selection may be an important driver in England[52]. Sundqvist et al[162] saw little reduction in trimethoprim resistance after drastic reductions in trimethoprim prescribing in Scandinavia, possibly due to co-selection[162]. This group and others have shown that trimethoprim resistance conferred via mutations in the dfrA gene carry little or no fitness cost, meaning they can persist in a population regardless of use or non-use of trimethoprim. Analogously, Egwuatu et al studied the effect of prolonged co-trimoxazole use in patients with HIV, and showed a significant increase in beta-lactam resistance in faecal flora isolated over a 12 month period[309].

5.5.5 **Analysis of associations between duration and resistance**

My analysis of the quantity of antibiotic exposure (in days of therapy) and risk of resistance is intriguing – in my dataset, I found that there was no evidence of additional increases in risk associated with increasing days of exposure, over and above a simple ever/never exposure effect, as might have been expected. This may be due to low power to detect these kind of quantitative effects, particularly as most individuals had received relatively short durations of antibiotics (IQR for days of therapy in prior year 1-9, and 1-6 for prior month) (**Table 36 and Table 39)**. Further, the true pattern of risk may not increase linearly on the log-odds scale, and my dataset may have been too small to detect e.g. thresholding effects. Alternatively, this lack of association may reflect a biological process,that any exposure to an antibiotic or class will increase risk, and additional days (at least the durations in my study) do not appreciably alter this risk. This bears further study, as, if replicated, suggests that current efforts to reduce duration of course may not have major impacts on resistance. More work is urgently needed to study associations between duration of therapy and resistance, as there is currently very

little evidence to link shorter, or longer durations, to resistance[91,92] except in one study of acute otitis media[104], and one subgroup analysis in a study of ventilator-acquired pneumonia[97] which both showed positive associations between resistance and longer courses of antibiotics.

5.5.6 Using 'Access/Watch' list classification of beta-lactams versus gram-negative-active beta-lactams

Amoxicillin and ampicillin are classified as beta-lactams with gram negative activity, though they are not classified as broad-spectrum beta-lactams according to the 'UK watch list'. I analysed exposure to broad-spectrum beta-lactams using both definitions, and found very little difference between the two – both showed significant associations with beta-lactam resistance in both exposure in prior year and prior month analyses. However, the reason for this was likely to be that relatively similar groups of patients were exposed with either definition. Adding in patients with a positive blood culture who had been exposed to amoxicillin, but who had not already been exposed to another broad-spectrum beta-lactam, changed numbers by only 9 and 2 individuals in prior year and prior month analyses respectively. As such I cannot draw significant meaningful conclusions about whether amoxicillin is best classified as broad or narrow-spectrum when analysing the association between spectrum of beta-lactam and association with resistance. When designing this study, I decided that splitting the analysis down to individual antibiotics would lead to too many small analyses overall, and that I would be more likely to identify antibiotic associations by using antibiotic group classifications.

Several previous studies, mostly much smaller than my study, have found associations between prior patient-level beta-lactam use and beta-lactam resistance in bloodstream infections due to Enterobacteriaceae (

Table 24). My study further supports this association, and additionally adds the new knowledge about different effects of narrow and broad-spectrum beta-lactams and duration/timing (last month vs year).

5.5.7 **Non-antibiotic risk factors associated with resistance**

It is probably unsurprising that previous (non-bloodstream) beta-lactam resistant infection was the strongest risk factor for resistant vs susceptible bloodstream infection – this likely represents colonisation, and the patient's flora containing resistant *E. coli* and *K. pneumoniae* isolates which presumably then caused invasive disease at a later stage. Alternatively, it could also be a downstream marker of prior antibiotic exposure. Whilst my model corrects for hospital antibiotic exposure, it does not account for community use (a major limitation, see below), and prior resistant infection may indicate the additional, unmeasured risk factor of high community antibiotic use.

The number of emergency admissions was also a strong predictor of resistant bloodstream infections, likely both a measure of exposure to resistant organisms through healthcare exposure, but also a measure of illness and comorbidity. Exposure to haematology/oncology wards similarly likely represents exposure to resistant isolates, and enhanced likelihood of immunosuppression due to chemotherapeutic agents and antibiotics. It is slightly harder to explain associations with congestive cardiac failure, but my experience in general medicine would suggest these patients frequently present to healthcare with shortness of breath, and are frequently covered for chest infections in case there is an infective element, and thus receive more antibiotics. Notably, community prescribing guidance in Oxfordshire for bronchitis recommends a first line of self-care and safety netting, but with the exception of those >80years of age who have been hospitalised in the prior year, have diabetes, *have congestive*

cardiac failure, have as serious neurological disorder or are on steroids[310]. This reflects the UK National Institute of Health and Care Excellence (NICE) guidance on prescribing for acute cough and bronchitis[311]. Hence associations with this specific co-morbidity may again represent unmeasured community antibiotic use, or there may be some other mechanism that predisposes heart failure patients to resistant infections.

Previous skin/soft tissue procedures were also a risk factor for resistant vs susceptible bloodstream infections - these were generally for abscess management, which are usually caused by skin organisms like staphylococci rather than gram negative bacteria. Again it is difficult to hypothesise a causal association with resistant vs susceptible *E. coli* or *K. pneumoniae* bloodstream infections, and again, these may be an indicator of unmeasured community antibiotic exposure.

It is interesting to note that gastrointestinal procedures such as endoscopy were not associated with resistant vs susceptible bloodstream infections in this study, whilst other work has linked them to the spread of carbapenem-resistant Enterobacteriaceae[312]. This may suggest that the endoscopy disinfection process used in the OUH is sufficient to fully sterilise the endoscopes and no transmission occurs, or that this route of colonisation is so infrequent, and hence not detectable in my sample size.

It is also interesting to note that the hospital frailty score, which I trialled as a method of measuring frailty using diagnostic coding, was not independently associated with resistant vs susceptible bloodstream infection. This may be because the simpler measure of number of emergency admissions was an effective measure of frailty. Using the codes linked to the admission performed better in terms of identifying independently predictive comorbidity (congestive cardiac failure): the Charlson score did not add independent information either. This may be because the main issue with using prior codes only is that patients who had not

had any interactions with the hospital in the prior year had no codes, and this caused significant loss of data.

On balance, it appears that using codes linked to matched admissions is a better measure of comorbidity than prior codes alone. It is possible that the combination of the two may out-perform either one alone. It also suggests that being able to link hospital and primary care databases would be of great assistance in measuring comorbidity, as this would remove the issue of non-interaction with hospitals leading to loss of data, as well as enabling use of community antibiotic prescribing data (see below).

5.5.8 **Strengths and limitations**

This is the largest study to date of factors associated with resistant vs susceptible *E. coli* and *K. pneumoniae* bloodstream infections. Study strengths include detailed patient-level antibiotic exposure data and the ability to verify from these records that the patient received an antibiotic, unlike prescription data, which a patient may not have taken. I was able to correct for a wide range of health status measures. I have also been able to compare intravenous and oral antibiotics due to detailed prescribing information. Whilst missing data can be a major issue in electronic health record studies, this study was not significantly affected, due to most bloodstream isolates being successfully linked to a complete set of administrative data (993/1043, 95%).

Limitations include the single centre nature of the study. However, the most important limitation is that I have only been able to measure in-hospital exposure to antibiotics, rather than total community and inpatient exposure. Hospitals account for around 18% of total antibiotic use[313], but around 65% of broad-spectrum antibiotic use[268]. Thus my study may have missed associations between commonly-used primary care narrow-spectrum antibiotics

and beta-lactam resistant vs susceptible bloodstream infections. The implicit assumption is that the effects of any commonly used community antibiotics will be captured through effects of hospital antibiotics or other confounders I have adjusted for.

Clearly a study which has both detailed patient-level data on community and hospital use would be optimal, but current UK data protection regulations mean it is challenging to set up a research database which is able to link community (GP and community hospital data) and hospital data. Some databases like the UK National Cancer Data Repository are showing this can be possible, and it would be of great assistance to future research in antimicrobial resistance to establish these with data on community level antibiotic use linked to hospital use and microbiology. Alternatively it may be possible to link community pharmacy community dispensing data to hospital data. I have used diagnostic codes to measure comorbidity rather than objective clinical criteria – in a study of this size, reviewing patient notes was not possible with my resources. I was not able to measure proton pump inhibitor use, as this data was not available in the linked database at this time, or travel to foreign countries, an acknowledged risk factor for carriage of resistant organisms[314,315]. Whilst I had data on previous microbiology cultures, in Oxfordshire, rectal screening for resistant Enterobacteriaceae is rarely performed due to low current prevalence of carbapenem-resistant organisms.

I was unable to meaningfully test associations with rarely-used antibiotics in my hospital, such as tetracyclines, quinolones and clindamycin, due to the study size; however, given their rare use, even strong associations would still make a relatively small contribution to the risk of developing resistant vs susceptible bloodstream infections. I also did not look at time since last antibiotic exposure, which has been associated with risk of resistance in previous studies[316].

It is also possible that different relationships between antibiotic exposure and resistance exist for *E. coli* and *K.pneumoniae* bloodstream infections, or that the non-antibiotic factors associated with resistance may differ. However the number of patients with *K. pneumoniae* isolates was substantially smaller than those with *E.coli* isolates, and it was not feasible within the timescale of this thesis to explore the question in detail. Another limitation is that I did not include measures of disease severity or biomarkers into my analysis. Whilst this data was theoretically available, the time resources available were not sufficient to incorporate biomarkers such as the white cell count, CRP or lactate due to the amount of data cleaning required, and need to deal with missing data by using methods such as imputation.

I also did not include time in hospital prior to blood culture collection as a risk factor in my model. This was a risk factor that was not present in previous studies, but identified during discussion with thesis examiners. Subsequent analysis revealed that individuals with a resistant isolate had spent significantly longer as an inpatient (during the matched admission) than individuals with a susceptible isolate – although the absolute difference was small (~30 mins). It is possible that adding this variable to the multivariate model may have improved the model fit, but the small absolute difference between groups reduces the chance that associations between antibiotic exposure and resistance that existed were missed as a consequence of not including this variable.

Finally, whilst I have attempted where possible to measure risk factors in the most robust way possible from electronic health record data (such as using ward-stay data rather than recorded consultants), I have not formally validated the predictive ability of my strategies to identify clinical entities, such as the codes representing the Charlson score comorbidities. Instead I have made the assumption that the accuracy of coding in my dataset resembles that of previously published studies suggesting that the positive predictive value of diagnostic codes in identifying Charlson comorbidities is around 82-100%[204]. My work in Chapter 3 suggests

this is a reasonable assumption. Equally, I do not know the predictive ability of a prior catheter-specimen urine in identifying patients with a previous catheter, or prior admission or discharge from care homes in identifying patients in long term care facilities. In almost all of these cases, the coding strategy I have used would result in the under-identification of risk factors, and hence risk factors that may contribute to resistant vs susceptible bloodstream infections being erroneously excluded from the final multivariate model due to dilution bias in estimating their effects. This may either lead to a type I error, where unmeasured (or here incompletely adjusted for) confounding means that a relationship between antibiotics and resistant vs susceptible bloodstream infection is found in statistical models but is in reality due to differences in the patient populations that have not been accounted for in the model. It may also theoretically lead to a type II error, where the non-inclusion of risk factors leads to a poorer model which fails to find statistical significance of important antibiotic factors. However, I had a very large number of factors that I hypothesised could plausibly affect the risk of developing a resistant vs susceptible bloodstream infection, and including them all in a full multivariable model would also have reduced power to detect genuine effects.

5.5.9 **Implications**

These findings provide at least some support to efforts to restrict use of broad-spectrum beta-lactams in efforts to reduce antibiotic resistance in clinically important bloodstream infections, and the policy of restricting beta-lactam use according to the UK 'Watch' and 'Access' categories. Of note, the UK classifies co-amoxiclav as a 'Watch' antibiotic, whilst the original WHO classification has it as an 'Access' antibiotic. I have followed the UK version as it has most relevance to local patterns of antibiotic use, and stewardship decisions. Repeating my analysis using the international WHO categorisations may lead to different conclusions.

This study highlights that more research is needed to assess whether there are associations between duration of therapy and risk of resistant vs susceptible bloodstream infections, to provide an evidence base (or not!) for stewardship activities designed to reduce duration of therapy. It also highlights the need to further investigate the effects of swapping intravenous for oral therapy on selective effects for organisms that colonise the gut.

However, if cross-resistance and co-selection are contributory mechanisms, this suggests that changes in antibiotic formulary that increase use of trimethoprim and/or co-trimoxazole, often as a beta-lactam sparing strategy, may actually do very little to reduce, or may in fact even increase, resistance to beta-lactams in Enterobacteriaceae.

5.6 **Conclusions**

In an analysis of beta-lactam–resistant vs susceptible bloodstreams caused by *E. coli* or *K. pneumoniae*, hospital broad-spectrum beta-lactam exposure in the prior year, and any oral antibiotic, beta-lactam, broad-spectrum beta-lactam, narrow-spectrum beta-lactam given orally, and anti-folate antibiotics in the prior month were associated with beta-lactam resistant bloodstream infections. No association between days of therapy and increased risk of resistance was found. It suggests that non-linear effects, pharmacodynamics profiles, and cross resistance may play significant roles in complex in-vivo interactions that determine the effects of antibiotics administered on an individual's subsequent risk of resistant infection. It also provides some support to the hypothesis that reducing use of broad-spectrum beta-lactams (on the UK 'Watch' list) may reduce selection for beta-lactam resistance in serious infections caused by Enterobacteriaceae.

6 CONCLUSIONS AND FUTURE WORK

This thesis commenced with the aim of identifying prescribing strategies relevant to the acute medical physician which can reduce the spread of antimicrobial resistance, without adverse outcome.

6.1 Clinical implications to the acute physician

For the medical physician managing patients referred to general medical services in an acute, unselected take, it is impossible to be unaware of ongoing efforts to attempt to reduce antibiotic prescribing, and use less broad-spectrum antibiotic therapy. However, there is lack of clarity about how this can be achieved, and ongoing concerns that trying to reduce their prescribing, given the clinical uncertainty prevalent in the acute setting, may inadvertently lead to patients with serious bacterial infections being left untreated or undertreated.

The work in Chapter 2 identifies that it is possible to substantially reduce overall antibiotic consumption for acute, unselected medical inpatients, by up to a third, and start fewer patients on antibiotics, without any evidence of excess mortality or readmissions. However, it highlights that one strategy for achieving this reduction safely may be by holding antibiotics in cases of clinical uncertainty on patients who are not seriously unwell, but admitting them for observation. This ‘watch and observe’ strategy contrasts the alternative ‘prescribe and discharge’ strategy – where one avoids not treating serious infections by giving more patients antibiotics, using the prescription as the ‘safety net’.

The analysis supporting this phenomenon is based on relatively small numbers, and requires replication in larger studies. However, for the acute medical physician, this work highlights

that the decision over whether or not to prescribe in this setting is extremely challenging. It tells us that whilst studies suggest that around a third of antibiotics used in this setting may be inappropriate (when judged retrospectively[65,317]), telling physicians to simply 'use less' may lead to significant unintended consequences as people adapt their own patient management algorithms to maintain their own levels of acceptable patient safety and risk tolerance.

It may well be that the benefit of avoiding antibiotics, especially in patients at high risk of subsequent resistant infections, is worth the cost of a period of inpatient monitoring, both in terms of hospital costs and risk of infection from hospital exposure. The cost of treating resistant infections, especially recurrent infections once colonisation is established, is significant[318,319]. The cost to the patient of lost time and health due to resistant infections is substantial. But it is a cost that is hypothetical, dependent on multiple poorly-characterised factors, and challenging to calculate. Comparatively the cost of a hospital bed and overnight care is extremely well known and very concrete. It is hard to justify to senior management, or the clinical director, facing acute bed shortages and funding deficits prevalent in the current NHS, that the immediate financial and opportunity cost of admission is worth a small reduction in the risk of resistant infections in the future, though over a 20 year period it may make financial sense. The acute physician could be encouraged, from this work, to consider starting fewer patients on antibiotics in the setting of uncertainty where patients are well supported and have easy access to hospital in case of deterioration. Alternatively, they could be encouraged to consider the use of other strategies to provide the 'safety net' such as outreach nurses, telemedicine or remote monitoring, without need for antibiotics or admission.

It is important to note that even if the 'hold and observe' strategy contributed to the reductions in antibiotic initiation I observed, it was not possible to say whether this was the only reason. The acute physician could potentially achieve some reduction safely using

improved strategies to risk stratify patients. Other studies have suggested potential 'low hanging fruit' for achieving this safely may lie in uncomplicated respiratory tract infections[67] and patients with a concern about urinary tract infections[83-85].

The other findings from Chapter 2, that reduced broad spectrum use and shorter lengths of treatment may be possible without adverse clinical outcome, are probably more influential in providing support for more achievable changes in prescribing. Especially given good evidence from a number of systematic reviews that shorter courses have similar clinical outcome to longer ones, the acute physician should generally be encouraged in shortening durations of treatment. However given the recent study suggesting that there may be lower relapse rates when longer courses are used to treat cellulitis in a cohort of largely older adults, and a meta-analysis suggesting lower treatment failure rates for longer courses in otitis media, more work needs to be done to understand how to stratify patients and identify those at high risk of relapse, rather than simply treating large numbers of patients with long courses when most of them will not benefit from the increased duration. This could either be in identifying cohorts of patients at high/low risk based on factors at presentation, or based on treatment response. Identifying when it is safe to stop is a key area for future research to support reductions in antibiotic exposure.

The work in Chapters 4 and 5 on diagnostic coding for Charlson comorbidities and infective endocarditis respectively may have less relevance to the acute physician aiming to reduce resistance, but provide insights into the clinical coding process. To any physician who thinks the solution to coding inaccuracies is to simply 'get doctors to do it' (anecdotally, a common first response when coding issues are discussed), my findings suggest that actually the coding system is fairly robust, just as accurate as a reasonably knowledgeable medical doctor, and that when discrepancies between clinical diagnoses and codes are encountered this is only rarely due to errors by the coding team. It is, and much more commonly, a result of coding

implemented as a process designed primarily to capture clinical activity for purposes of reimbursement, rather than capturing a representation of a patient's clinical status.

The work in Chapter 5 examining prior antibiotics and association with beta-lactam resistance in *E. coli* and *K. pneumoniae* bloodstream infections provides some useful information to the acute physician to support antibiotic choice. In the setting where evidence is far from abundant, it suggests that efforts to reduce beta-lactam prescribing, and restrict WHO 'watch' list beta-lactams particularly[119], may assist in reducing a patient's subsequent risk from resistant infection. Whilst the findings require replication in further studies, it may just make the acute physician think twice about prescribing co-trimoxazole or trimethoprim as a beta-lactam-avoiding option to patients at high risk of beta-lactam resistant *E. coli* or *K.pneumoniae* infection, given both this study and others have found evidence for the possibility of cross-resistance and co-selection[52,162,309].

6.2 Clinical implications for individuals or organisations involved in setting or implementing hospital antibiotic guidelines

The work in Chapter 2 on antibiotic use in the acute setting supports the need for hospital guidelines to address issues beyond simple antibiotic choice, and also include more general guidance for appropriate risk stratification, taking into account clinical factors, to guide improvements in antibiotic use. Advice on when to prescribe antibiotics, rather than just what to prescribe, needs to address the significant issue that antibiotics are not just used when an infection is certain – they are frequently used in hospitals as 'safety nets' due to clinical uncertainty; reducing that uncertainty may alleviate some of this drive to prescribe.

The work in Chapter 2 also highlights the importance of measuring a range of clinical outcomes when evaluating projects that aim to change prescribing, especially if the aim is to

reduce the number of patients started on antibiotics. It highlights the importance of exploratory work, and consultation with stakeholders prior to widespread roll out of these projects, in thinking about the potential 'unintended consequences' and proactively aiming to measure them. An excellent example was the work by Bell et al[320] studying a change in surgical prophylaxis guidelines, leading to increased use of gentamicin. Concerns about possible subsequent increases in renal failure were raised, studied, found, and used to inform antibiotic policy changes.

The work on diagnostic coding in Chapters 4 and 5 serve limited relevance for those setting hospital antibiotic guidelines, beyond suggesting that if there is a wish to monitor outcomes of programmes using coding data from electronic health records, this should be done with input from individuals who have significant experience in coding and ideally be based on a validation study (even if small). Even if it is not intended for publication, the potential to get misleading results and draw erroneous conclusions is significant.

The work in Chapter 5 has some significance to those drafting guidelines. Primarily it is worth highlighting that it is a single study on one institution, and any findings probably need replication prior to reaching the level where they could be taken to influence antibiotic decision making. However they provide support for the use and integration of the UK 'Watch' list classification of antibiotics into hospital guidelines. The identification of an association between co-trimoxazole/trimethoprim exposure and beta-lactam resistance in *E. coli* and *K. pneumoniae* has been seen in previous UK studies, and this study provides another word of caution to trusts aiming to address beta-lactam resistance by using these antibiotics as 'beta-lactam-sparing' agents. More work is urgently needed to address this apparent association, as my experience discussing guidelines with clinicians from this and other hospitals is that co-trimoxazole is being seen as 'making a comeback' for precisely this reason, and it may be counterproductive if cross-resistance is prevalent. The lack of

significant association found between duration of prior exposure and risk of resistance is probably not strong enough a finding to impact on guidelines – there is a possibility that the lack of association seen was due to study design and size. Clearly more work needs to be done investigating the potential for reducing duration of antibiotic courses to lead to meaningful reductions in future resistance.

6.3 Implications for research studying antibiotic use and antimicrobial resistance

As noted above, the work in Chapter 2 highlights the importance of measuring more than just antibiotic use when studying the effect of antibiotic interventions. Whilst this Chapter additionally looked at mortality, length of stay, and infection-related complications and suggested attempts to reduce antibiotic exposure may have increased length of stay, this principle extends to resistance outcomes and resource implications. If the aim is to find interventions that are feasible, sustainable, and achieve their primary aim of addressing antimicrobial resistance, then it is important to acknowledge that antibiotic use does not exist in a bubble, but in a complex healthcare environment where the direct or indirect costs of changing prescribing behaviour may ultimately be greater than healthcare institutions are able to support, even if they do lead to the intended reductions in resistance. Assessing and reporting these other outcomes will greatly improve the ability of both researchers and clinicians to identify ways of achieving sustainable, effective change. Doing so also demonstrates the researchers' ability to see the wider picture, and address the potential concerns held by non-specialists and those in management with priorities other than antibiotic use.

It is worth acknowledging that the majority of studies of antibiotic interventions evaluate the effect in a single centre, or a few linked hospitals, and will be underpowered to detect

anything but quite large effects on mortality, or resistance. Whilst this might initially suggest there is limited utility in smaller studies looking at or publishing these outcomes, the data can be used in meta-analyses, which often highlight the lack of reporting of clinical or resource outcome[68].

The study size issue identified in Chapter 2 is worth discussing further. Certainly in the UK, resistant infection remains a relatively rare outcome for the general medical inpatient, and so studying it requires relatively large sample sizes, involving multiple institutions, if the aim is to meaningfully assess the effect of an intervention on resistant infection in this setting. Efforts to curate and improve national datasets of electronic health record data, including both microbiological data and prescribing, will be invaluable in future efforts, and should be prioritised. Alternatively, more common surrogate outcomes which are predictive of resistant infection, such as gut colonisation with resistant organisms, could be more widely considered as an outcome. However this would only be feasible in settings with high levels of sampling and testing in place on clinical grounds, given the ethical and resource challenges associated with research-based sampling; careful consideration would have to be given about sampling bias as well.

The work on Charlson comorbidities and diagnostic coding in Chapter 3 has limited implications for those studying antibiotic use and resistance more generally, serving mostly to reinforce existing use of diagnostic coding as a reasonable method of correcting for comorbidity as a confounder in electronic health record studies. It provides a small amount of new knowledge - that using codes assigned on discharge as a proxy for admission comorbidity is robust, and that it is relatively rare for codes to represent conditions that were not present upon admission.

Chapter 4 provides one of the most in-depth evaluations of the relationship between diagnostic codes and confirmed clinical cases of infection currently available, using infective endocarditis as a case study. It highlights the importance of validating the accuracy of diagnostic codes when they are used for epidemiological purposes rather than the administrative reimbursement they were designed for, and provides clear methods that future studies can employ to improve case identification from electronic health record data. It highlights to the researcher without in-depth experience of the clinical coding process that a diagnostic code does not equal a clinical case, and failure to understand the reasons why a diagnostic code may be applied, or at the very least conduct a simple 'sanity check' of coding data, can lead to extremely misleading results. The exploration of secondary/supplementary diagnostic codes for infecting organisms and their relationship to the causative organism found on microbiological testing shows that whilst these secondary codes are relatively robust, they probably have to be used only with extreme caution to study changes in infection patterns in time series data, and close examination of changes in coding behaviour is needed. They are probably reasonable to use to reflect proportions of codes assigned to different organisms. Using diagnostic coding alone to assess microbiological outcomes in antibiotic intervention studies therefore should be done with caution when this covers substantial periods of time and/or institutions. Realistically, a better solution would be to pursue efforts to link microbiology data to electronic health record data.

The work in Chapter 5 looking at prior antibiotic exposure in resistant vs susceptible bloodstream infections identifies a number of avenues worth pursuing for the researcher studying antibiotic use and resistance. It confirms the link between beta-lactam prescribing and resistance, and suggests some utility in pursuing analyses based on the WHO access/watch/reserve classifications. It identifies a potential cross-resistance phenomenon, with prior trimethoprim/co-trimoxazole exposure being associated with beta-lactam

resistance, as suggested by previous studies[52,53,162]. This underlines the importance of antibiotic/resistance studies looking beyond resistance to the antibiotic of focus, and considering the impact on resistance to other agents, and vice versa. Otherwise it is more than possible that vast resources may be employed in changing antibiotic prescribing that may ultimately be futile. The identification of a different impact of intravenous compared to oral preparations also suggests the need for further exploration. Current UK efforts in antimicrobial stewardship are firmly focused on earlier switching from intravenous to oral antibiotics. If oral antibiotics carry with them a higher subsequent risk of resistant infection, a phenomenon only previously investigated in detail in mouse models to my knowledge, it is worth considering and quantifying this increase in risk, and considering whether the resource implications of more intravenous treatment are worth the long term benefit. Additionally, it suggests that exploring methods of drug delivery that avoid exposure of gut flora may be productive. As discussed above, the lack of association found between duration of exposure and risk of resistance requires replication in other studies.

Finally, the work demonstrates the utility of linked microbiology, prescribing, and administrative electronic health record data. However a key limitation of this, and other, similar, studies is the fact that only hospital or primary care prescribing has been studied, not both, leaving a significant unmeasured confounder of unaccounted-for antibiotic exposure. It highlights that that more efforts to integrate hospital and primary care datasets are urgently needed to enable more robust large-scale analyses of the associations between antibiotic exposure and resistance.

6.4 **Summary**

This D.Phil. has made small steps forward in the knowledge that the acute physician can employ to try and minimise the risk of resistant infection to the patient they treat, and the population as a whole. In a setting where evidence is so limited, I believe that even small steps are of some use. To guideline writers, it suggests a word of caution in using trimethoprim/co-trimoxazole as beta-lactam sparing agents, support for use of the WHO Access/Watch/Reserve classifications to guide antibiotic choices, and the need for more decision support around the decision whether or not to prescribe. To researchers using electronic health record data, it provides a useful demonstration of the value of careful study design, and a few examples as to how to achieve this. And to researchers studying antibiotic use and resistance, it generates some interesting hypotheses to take forward to larger studies – the importance of addressing cross-resistance, the need to look at intravenous versus oral preparations, and further exploration about the relative impact of duration of treatment.

Work is progressing on developing national datasets of electronic health record data such as linking the Health Episodes Statistics (HES) data from NHS Digital in England together with microbiology data from the Second Generation Surveillance System held by Public Health England and antibiotic prescribing data from both commercial sources such as IQVIA and NHS Business. Developing, maintaining and curating these datasets is essential in assisting high quality research in a wide range of areas. Efforts to integrate primary care data also need to be prioritised. With these efforts, it becomes increasingly feasible to conduct large-scale multi-centre analyses which can aim to meaningfully assess the impact of antibiotic prescribing strategies on resistance across the entire health economy. The work of this thesis provides some guidance into how these studies might be robustly designed, and what research questions might be prioritised. The insights these studies generate can be applied

subsequently with the aim of rationally altering how antibiotics are used in hospitals and beyond, to minimise the spread of antimicrobial resistance[65].

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